SYMPOSIUM ON THE ULCER PROBLEM

Vol. 17 MAY, 1945 No. 5

COPYRIGHT DEPOSIT

SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

JUL 10 1945

EDITORS

ALTON OCHSNER, New Orleans OWEN H. WANGENSTEEN, Minneapolis

ASSOCIATE EDITOR

ALFRED BLALOCK, Baltimore

CONTENTS

Original Communications

Symposium on the Ulcer Problem

A Direct Visual Technique for Studying Chemical and Other Injury to Exposed Mucosal Surfaces. Fred Kolouch, Jr., M.D., Minneapolis, Minn. ---- 641

The Pathogenesis of Caffeine-Induced Ulcers. J. A. Roth, M.B., Ph.D., and A. C. Ivy, Ph.D., M.D., Chicago, Ill. ---- 644

Influence of Caffeine on Ulcer Genesis. K. Alvin Merendino, M.D., Edward S. Judd, M.D., Ivan Baronofsky, M.D., Sidney S. Litow, M.D., Bernard G. Lannin, M.D., and Owen H. Wangensteen, M.D., Minneapolis, Minn. ---- 650

The Pedicled Jejunal Transplant Onto the Gastric Wall. Fred Kolouch, Jr., M.D., Alfonso T. S. Dubus, M.D., and Owen H. Wangensteen, M.D., Minneapolis, Minn. ---- 667

An Attempt to Confirm the Alleged Inhibitory Effect on Gastric Secretion of Jejunal Pedicle Grafts in the Wall of the Stomach. M. I. Grossman, Ph.D., M.D., D. F. Dutton, B.S., and A. C. Ivy, Ph.D., M.D., Chicago, Ill. ---- 685

The Indications for Operation in Cases of Peptic Ulcer From the Internist's Point of View. Arthur L. Bloomfield, M.D., San Francisco, Calif. ---- 692

The Medical Treatment of Peptic Ulcer Refractory to Sippy Therapy. Asher Winkelstein, M.D., Albert Cornell, M.D., and Franklin Hollander, Ph.D., New York, N. Y. ---- 696

The Treatment of Perforated Duodenal Ulcers. Roscoe R. Graham, M.B., Toronto, Canada, and Major E. B. Tovee, Royal Canadian Army Medical Corps ---- 704

Experimental Evaluation of a Satisfactory Operation for Ulcer. B. G. Lannin, M.D., Minneapolis, Minn. ---- 712

Removal of the Vagus Innervation of the Stomach in Gastroduodenal Ulcer. Lester R. Dragstedt, M.D., and Paul W. Schafer, M.D., Chicago, Ill. ---- 742

Gastric Ulcer and Cancer. Arthur W. Allen, M.D., Boston, Mass. ---- 750

A Synthetic Predigested Aliment for Jejunostomy Feeding. Franklin Hollander, Ph.D., Stephan Rosenak, M.D., and Ralph Colp, M.D., New York, N. Y., with the technical assistance of Ruth F. Karelitz, M.A. ---- 754

Editorial

Peptic Ulcer. Alton Ochsner, M.D., New Orleans, La. ---- 770

Books Received ---- 772

Published by THE C. V. MOSBY COMPANY, St. Louis, U. S. A.

Copyright 1945 by The C. V. Mosby Company

JUL -8 1945

SURGERY

ADVISORY COUNCIL

DONALD C. BALFOUR, Rochester, Minn.
VILRAY P. BLAIR, St. Louis
BARNEY BROOKS, Nashville
ELLIOTT C. CUTLER, Boston
WILLIAM E. GALLIE, Toronto
EVARTS A. GRAHAM, St. Louis
HOWARD C. NAFFZIGER, San Francisco
HARVEY B. STONE, Baltimore
ALLEN O. WHIPPLE, New York City

EDITORIAL BOARD

FREDERICK A. COLLER, Ann Arbor
EDWARD D. CHURCHILL, Boston
VERNON C. DAVID, Chicago
LESTER R. DRAGSTEDT, Chicago
RALPH K. GHORMLEY, Rochester, Minn.
ROSCOE R. GRAHAM, Toronto
SAMUEL C. HARVEY, New Haven
FRANK HINMAN, San Francisco
EMILE F. HOLMAN, San Francisco
EDWIN P. LEHMAN, University, Va.
FRANK L. MELENEY, New York City
JOHN J. MORTON, Rochester, N. Y.
THOMAS G. ORR, Kansas City, Kan.
GEORGE T. PACK, New York City
WILDER G. PENFIELD, Montreal
ISIDOR S. RAVDIN, Philadelphia
WILLIAM F. RIENHOFF, JR., Baltimore

COMMITTEE ON PUBLICATIONS

ARTHUR W. ALLEN
Boston, Mass.

CLAUDE S. BECK
Cleveland, Ohio.

ELEXIOUS T. BELL
Minneapolis, Minn.

ISAAC A. BIGGER
Richmond, Va.

ALBERT C. BRODERS
Rochester, Minn.

J. BARRETT BROWN
St. Louis, Mo.

ALEXANDER BRUNSCHWIG
Chicago, Ill.

LOUIS A. BUIE
Rochester, Minn.

WARREN H. COLE
Chicago, Ill.

C. D. CREEVY
Minneapolis, Minn.

GEORGE M. CURTIS
Columbus, Ohio

M. DE BAKEY
New Orleans, La.

JOHN STAIGE DAVIS
Baltimore, Md.

WILLIAM J. DIECKMANN
Chicago, Ill.

DANIEL C. ELKIN
Atlanta, Ga.

WILLIS D. GATCH
Indianapolis, Ind.

CHARLES F. GESCHICKTER
Baltimore, Md.

J. SHELTON HORSLEY
Richmond, Va.

J. MASON HUNDLEY, JR.
Baltimore, Md.

ANDREW C. IVY
Chicago, Ill.

DENNIS E. JACKSON
Cincinnati, Ohio

J. ALBERT KEY
St. Louis, Mo.

CHAUNCEY LEAKE
San Francisco, Calif.

FRANCIS E. LEJEUNE
New Orleans, La.

HAROLD I. LILLIE
Rochester, Minn.

JOHN S. LUNDY
Rochester, Minn.

FRANK C. MANN
Rochester, Minn.

CHARLES W. MAYO
Rochester, Minn.

ROBERT L. PAYNE
Norfolk, Va.

LEO G. RIGLER
Minneapolis, Minn.

ERNEST SACHS
St. Louis, Mo.

ARTHUR M. SHIPLEY
Baltimore, Md.

ALBERT O. SINGLETON
Galveston, Texas

MAURICE B. VISSCHER
Minneapolis, Minn.

RALPH M. WATERS
Madison, Wis.

JAMES C. WHITE
Boston, Mass.

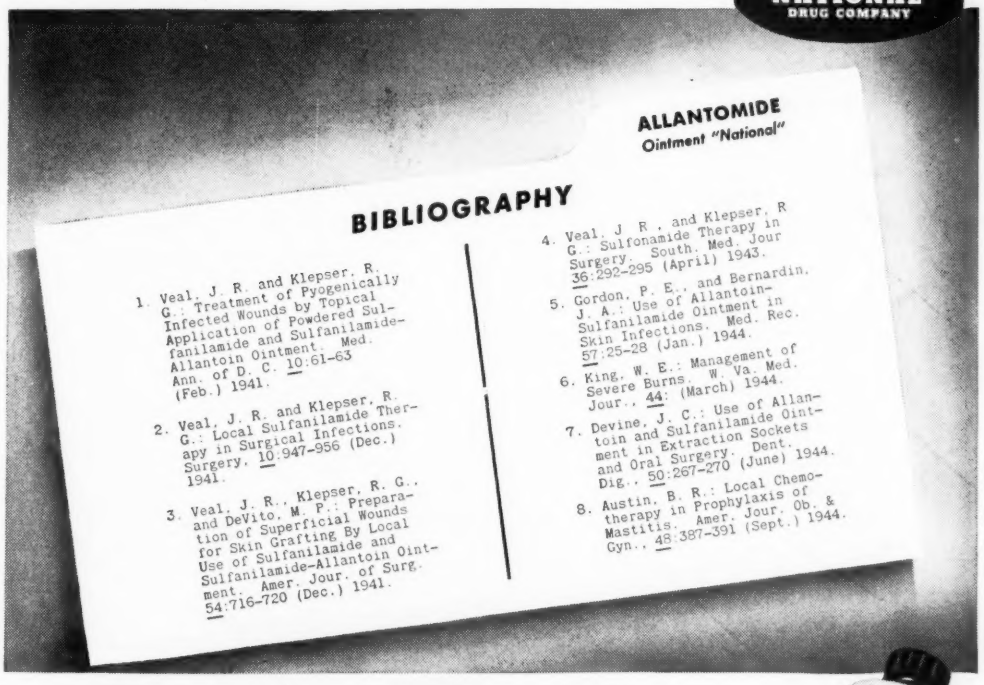
PHILIP D. WILSON
New York, N. Y.

JOHN A. WOLFER
Chicago, Ill.

Vol. 17, No. 5, May, 1945. Surgery is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. Subscription price: United States, its possessions, Pan-American Countries, $10.00 a year; Canada, $11.50 (Canadian Currency); Foreign, $11.00. Entered as Second-Class Matter January 20, 1937, at the Post Office at St. Louis, Missouri, under the Act of March 3, 1879. Printed in U. S. A.

BIOLOGICALS, BIOCHEMICALS, PHARMACEUTICALS FOR THE MEDICAL PROFESSION

NATIONAL DRUG COMPANY


ALLANTOMIDE
Ointment "National"
BIBLIOGRAPHY
1. Veal, J. R. and Klepser, R. G.: Treatment of Pyogenically Infected Wounds by Topical Application of Powdered Sulfanilamide and Sulfanilamide-Allantoin Ointment. Med. Ann. of D. C. 10:61-63 (Feb.) 1941.
2. Veal, J. R. and Klepser, R. G.: Local Sulfanilamide Therapy in Surgical Infections. Surgery, 10:947-956 (Dec.) 1941.
3. Veal, J. R., Klepser, R. G., and DeVito, M. P.: Preparation of Superficial Wounds for Skin Grafting By Local Use of Sulfanilamide and Sulfanilamide-Allantoin Ointment. Amer. Jour. of Surg. 54:716-720 (Dec.) 1941.
4. Veal, J. R., and Klepser, R. G.: Sulfonamide Therapy in Surgery. South. Med. Jour 36:292-295 (April) 1943.
5. Gordon, P. E., and Bernardin, J. A.: Use of Allantoin-Sulfanilamide Ointment in Skin Infections. Med. Rec. 57:25-28 (Jan.) 1944.
6. King, W. E.: Management of Severe Burns. W. Va. Med. Jour., 44: (March) 1944.
7. Devine, J. C.: Use of Allantoin and Sulfanilamide Ointment in Extraction Sockets and Oral Surgery. Dent. Dig., 50:267-270 (June) 1944.
8. Austin, B. R.: Local Chemotherapy in Prophylaxis of Mastitis. Amer. Jour. Ob. & Gyn., 48:387-391 (Sept.) 1944.

Positive Proof!

More and more physicians are proving the value of the allantoin-sulfanilamide combination in a hydrophilic ointment for use in daily practice as well as in controlled clinical trials.

Allantomide ointment is available for immediate use. It is easily applied with spatula after the usual technique of debridement. It does not cake nor stain. It is odorless and does not form a thick eschar to inhibit motion. Being water-miscible, the active agents in the specially developed non-greasy base are made available to mix with the aqueous secretions.

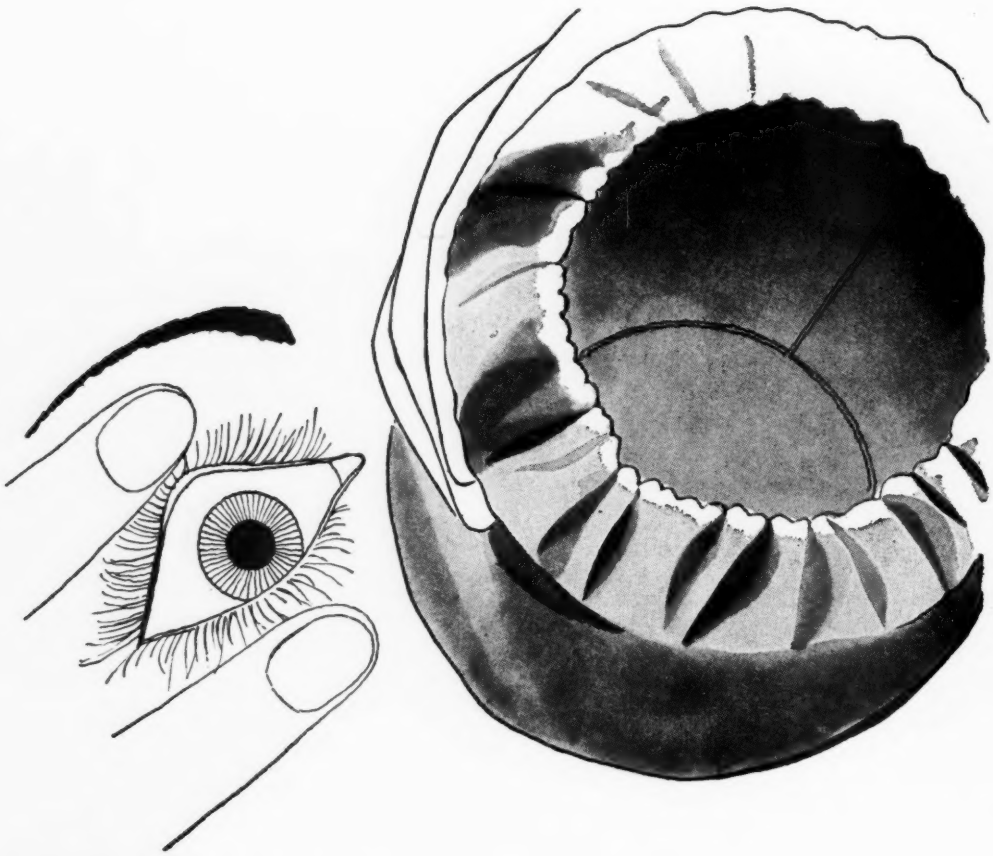
Indications: external ulcers, infected wounds or burns and chronic pyogenic infections of the skin, susceptible to the action of sulfanilamide. Write for literature. **The National Drug Company, Philadelphia 44, Pa.**

A NATIONAL 2 in 1 PREPARATION

Allantomide OINTMENT

(2% allantoin, 10% sulfanilamide in a non-greasy, water-miscible base)

OTHER ALLANTOMIDE PREPARATIONS: Allantomide Vaginal Cream Allantomide Liquid with Ephedrine • Sulfonamets • Allantomide Film



Still the Standard

"Diethyl ether remains the standard drug for inhalation anesthesia, because of its wide margin of safety, relatively low toxicity, economy and ease of administration, especially by the open drop method."*

For over 87 years, surgeons all over the world have depended on Squibb Ether, confident of its purity, uniformity and efficacy.

SQUIBB Ether

*Zentgraf, L. P., and Eversole, V. H.: Medical Progress: General Anesthesia: New Eng. J. Med. 229:437 (Sept. 9), 1943.

MANUFACTURING CHEMISTS TO THE MEDICAL PROFESSION SINCE 1858

FROM AN ORIGINAL ETCHING BY ERNEST D. ROTH

EDINBURGH UNIVERSITY SCHOOL OF MEDICINE—The teaching of medicine and surgery at this world-famous school began in the year 1503. Thus, behind the prestige it enjoys today stand nearly four hundred and fifty years of research, scholarship and clinical study. Of the many medical figures whose efforts helped to enhance the reputation of Edinburgh, the names of the first Alexander Munro, pioneer anatomist, and the immortal Sir Joseph Lister stand out. Closely associated with this school is the Royal Infirmary.

Education is the keystone of progress in the field of surgery. Indeed, the surgeon's skill and experience must be built on the foundation of knowledge and training. And in turn, the suture manufacturer's service to the surgical profession must be based on supplying new and carefully documented information on sutures as well as the production of sutures themselves. Outlined on the following pages are some of the services by which Davis & Geck constantly adds to the reservoir of suture data.

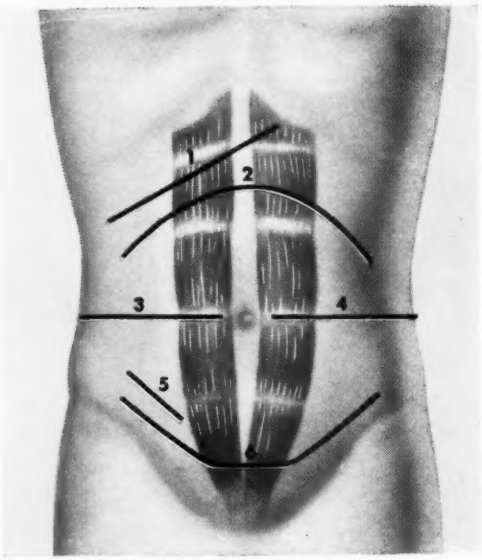
NUMBER TWO OF A SERIES

Incisions that Minimize Wound Disruption

AN IMPORTANT ADVANCE IN THE TECHNIC OF SUTURING

The employment of operative incisions which offer maximal assurance against sutures pulling through the tissues eliminates one of the principal causes of wound disruption and lessens the possibility of post-operative herniation.

Sutures hold most securely if the connective tissues within the wound are approximated in such a manner that the sutures must pull against the fibres within these layers. This necessitates cutting the connective tissues parallel to the direction of their fibres which, in the anterior abdominal wall, is usually best accomplished through a transverse initial skin incision.

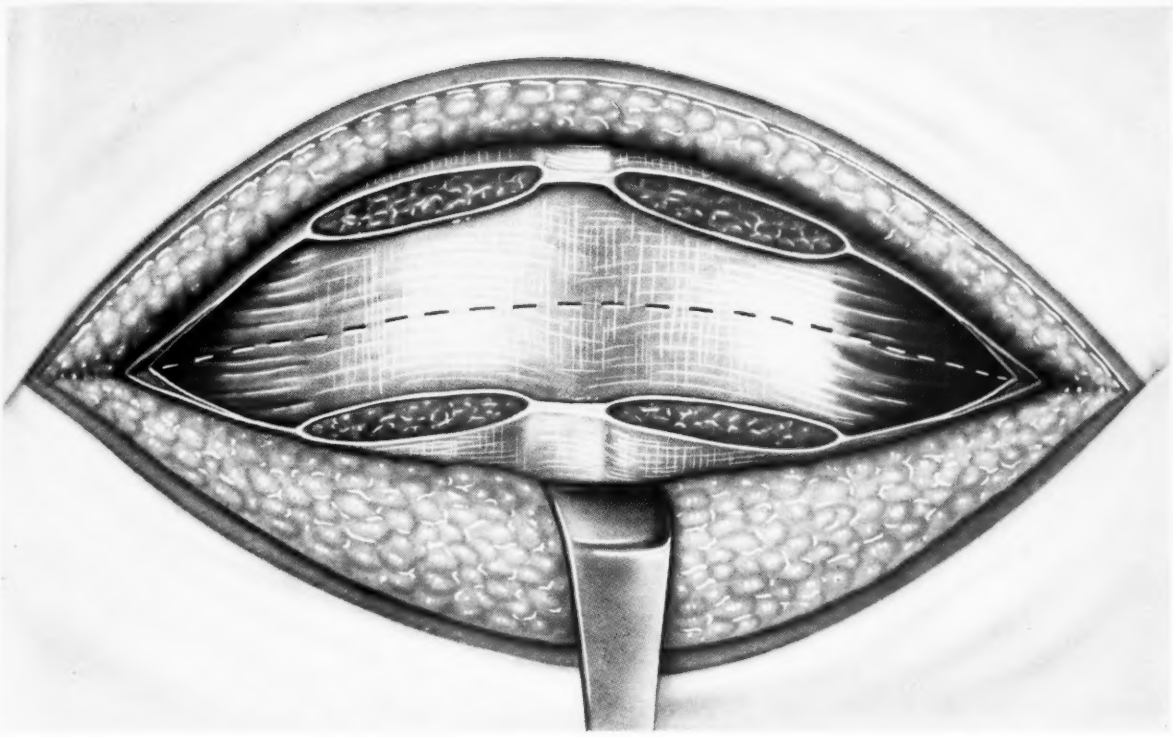


1. For gall bladder, common duct, head of pancreas.
2. Resection of stomach, transverse colon.
3. Resection of ascending colon, cecum, right sided lesions.
4. Descending colon, spleen and left sided lesions.
5. Appendectomy.
6. Pelvic surgery, resection of sigmoid.

In the past, transverse abdominal incisions have not found wide acceptance because they necessitate cutting across muscles in which sutures hold poorly and almost invariably cause tissue necrosis.

In the new technic of suturing transverse incisions, no attempt is made to suture muscle—only the surrounding sheath. Approximation of the muscle edges is further aided by keeping the patient in a semi-reclining position with knees partially flexed.

Because of the favorable results attending increasing use of this technic, and the current interest in principles which may facilitate early ambulation, D&G will present a series illustrating the incisions, and methods of suturing them.

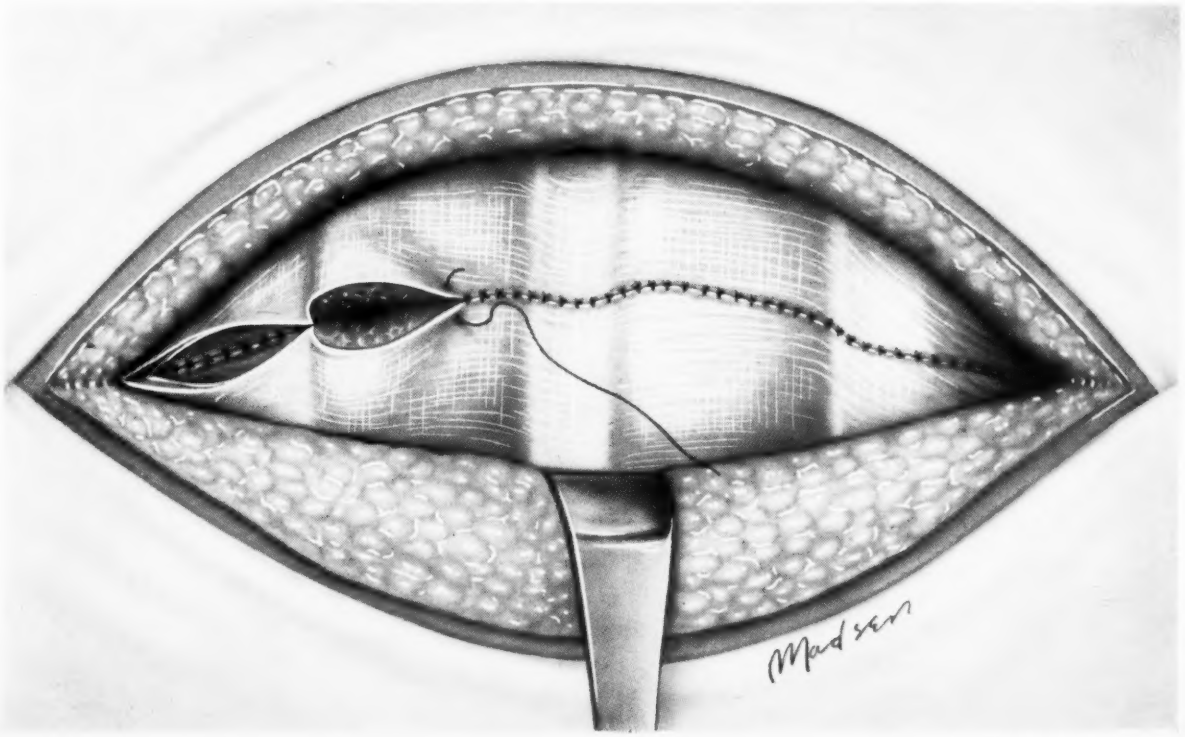


INCISION FOR GASTRECTOMY OR RESECTION OF TRANSVERSE COLON

Shaped like an inverted "U" with limbs parallel to the rib margins, this long incision is made transversely across the upper abdomen midway between xiphoid and umbilicus. Both recti are cut across. The posterior sheath and peritoneum are divided transversely or parallel to the fibers of the posterior sheath. The falciform ligament is divided and ligated. Excellent exposure of both the cardia and the pylorus of the stomach is obtained.

The incision is closed by placing interrupted sutures in the peritoneum and the posterior sheath. The sutures in the posterior sheath pull against the fibers, providing the repair with great strength. No sutures are placed in the muscle.

The anterior sheath is closed with interrupted sutures. No sutures are used in the fat. The skin is closed in the usual manner.



Sutures for Every Surgical Situation

Announcing

A NEW D&G PRODUCT

Surgaloy Metallic Sutures

Surgaloy* metallic sutures are the result of six years' extensive research and clinical observation in the development of a wire strand that would offer greater strength and ease of handling while conforming in all other respects to the highest requirements of the surgical profession for sutures of this type.

As part of this thorough investigation by D&G, a complete study was made of suitable metals including nickel, silver, tantalum, palladium, chromium, steel and various alloys. These were tested for pliability, tensile strength, tendency to kink, breakage due to kinking, facility of knot tying, magnetism, corrosion resistance, electro-passiveness in body fluids, inertness and toleration by the tissues.

Surgaloy, reflecting the properties of its components—chromium, nickel, steel and other ductile metals, offers these advantages:

1. Exceptional strength permits the use of very fine sizes.
2. Flexibility and freedom from kinking facilitates handling and tying.
3. Non-corrosive and inert: hence, minimal tissue reaction.
4. Non-magnetic and electro-passive in tissue fluids, it in no way restricts the use of diathermy or X-ray therapy.

Surgaloy sutures are armed with swaged-on Atraumatic needles specially designed for procedures in which metallic sutures are used. These are supplied in hermetically sealed glass tubes, heat-sterilized, ready for use.

The range of suture sizes and needle designs available provide efficient suture-needle combinations for surgery of nerves, tendons, thyroid gland, cleft palate and hare-lip, for hernioplasty, intestinal, plastic and orthopedic surgery, for closure of fascia and peritoneum and as dermal and tension sutures.

Reg. U. S. Pat. Off.

DAVIS & GECK, INC.
57 WILLOUGHBY STREET
BROOKLYN 1, NEW YORK

TO STIMULATE HEALING

Topical application of White's Vitamin A & D Ointment is a clinically accepted procedure of proven therapeutic value. Indicated to promote healthy granulation and epithelization in burns of any degree or location, crushing and avulsive soft tissue injuries, all types of indolent ulcers and slow-healing wounds.

White's

VITAMIN A AND D OINTMENT

presents natural vitamins A and D in the same ratio found in cod liver oil, in a soothing, lanolin-petrolatum base. It is free from unpleasant odor, excessive oiliness and will not stain or become rancid.

Ethically promoted — not advertised to the laity. White Laboratories, Inc., Pharmaceutical Manufacturers, Newark 7, N.J.

Available in four convenient sizes: 1.5 oz. tubes, 8 oz. and 16 oz. jars, 5 lb. containers.

℞

White's PRESCRIPTION vitamins

THREE
TEN-THOUSANDTHS
OF AN INCH
The erythrocyte, probably the most vital 3/10,000 of an inch, is subject to wide variation in size, form, and color in the anemias. 'Tabloid' 'Ferad' No. 2 is a clinically proved agent for the treatment of iron-deficiency anemias. The most effective therapeutic form of iron—ferrous sulfate (Ferrous Sulfate, Anhydrous gr. 2⅗) is provided together with sodium carbonate (Sodium Carbonate, Anhydrous gr. 1⅘) for optimal gastric tolerance.
'TABLOID'
'FERAD' #2
Bottles of 100 and 500
'Tabloid' and 'Ferad', Registered Trademarks

BURROUGHS WELLCOME & CO. (U.S.A.) INC., 9-11 East 41st St. • New York 17

Dawn of a New Era

IN 1894 practical immunology in America took its first great lifesaving step when the Mulford Biological Laboratories of Sharp & Dohme produced commercially the first diphtheria antitoxin.

Pilling's contribution to this great event was the manufacturing, in collaboration with the H. K. Mulford Co., of the first antitoxin syringe. The consequent rapid rise of practical immunology from this small beginning, followed by phenomenal strides in preventive medicine, is a mighty tribute to the medical profession and their co-workers, the manufacturers of biological products.

Developments and improvements have also marked Pilling progress for 131 years. The addition of the Bowles diaphragm chest piece to the stethoscope; a new process for making a lighter and stronger speculum—these are a few of the many Pilling contributions to the advancement of medical science.

This long history of continued development and manufacture of fine medical equipment is one reason physicians and surgeons think of Pilling when they think of instruments and supplies. George P. Pilling and Son Company, Philadelphia 3, Pa.

INSTRUMENTS BY—

Pilling

INSTRUMENT CRAFTSMEN SINCE 1814

SUGGESTED INSTRUMENTS

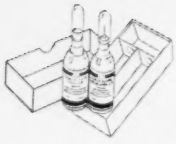
Illustrated Top to Bottom

P 15280	Hudson cranial drill set	$65.00
P 15385	Kolodny scalp hemostat	4.50
P 15153	Frazier brain retractor	9.50
P 15615	Cameron elevator	4.50

Order direct or from your supplier

Wyeth
REG. U. S. PAT. OFF.

PENICILLIN SODIUM WYETH



NOW AVAILABLE IN
THE
WYETH VIPULE
PENICILLIN PACKAGE

A Closed-System Unit
which provides

"Laboratory Fresh"
PENICILLIN SOLUTION

PENICILLIN SODIUM WYETH is prepared from carefully selected strains of certain Penicillium species. The concentrated solution of penicillin is immediately transferred to the special Wyeth VIPULE* in which it is reduced to a dry porous solid from the frozen state under high vacuum. The VIPULE is then rubber-stoppered, air-evacuated and flame-sealed.

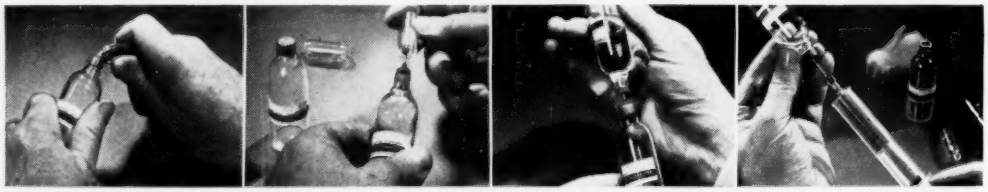
This form of packaging, exclusively Wyeth, provides prolonged protection for this sensitive antibiotic against air, moisture and other deleterious influences. Unbroken, the VIPULE guards the potency of the penicillin so efficiently that it remains stable for long periods of time.

REICHEL DIVISION
WYETH INCORPORATED
PHILADELPHIA 3, PA.

Wyeth

*REG. U. S. PAT. OFF.

The Vipule provides a closed system technique for preparing "Laboratory Fresh" penicillin solution



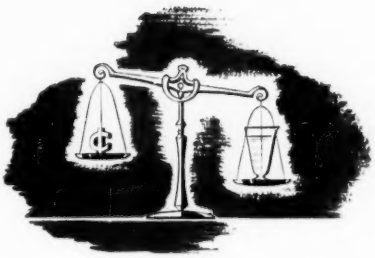
SOLUTIONS ARE PREPARED QUICKLY WITHOUT THE AID OF A SYRINGE

1. Snap the glass cap from the penicillin Vipule at the plainly visible etched groove. Turn down sleeve of rubber stopper over neck of Vipule.

2. Snap the glass cap from the Vipule of normal saline solution to expose the free end of the Vipule needle.

3. Invert vial portion of the Vipule with normal saline solution over the upright penicillin vial and push downward so that the ends of the needle penetrate both diaphragms.

"Laboratory Fresh" penicillin solution (5,000 units per cc.) is now ready to be withdrawn into a sterile syringe for administration.



MORE THAN MEASURES UP
...AT LESS THAN AVERAGE COST

● The new increased potency of Biomines Capsules more than measures up to the National Research Council's recommended daily vitamin allowances, providing a surplus in most cases. The cost of Biomines remains low, enabling patients to save as much as 40% of the cost of comparable products.

BIOMINES CAPSULES

MULTIPLE VITAMINS

B Complex Capsules

Frederick Stearns & Company
Division
DETROIT 31, MICHIGAN

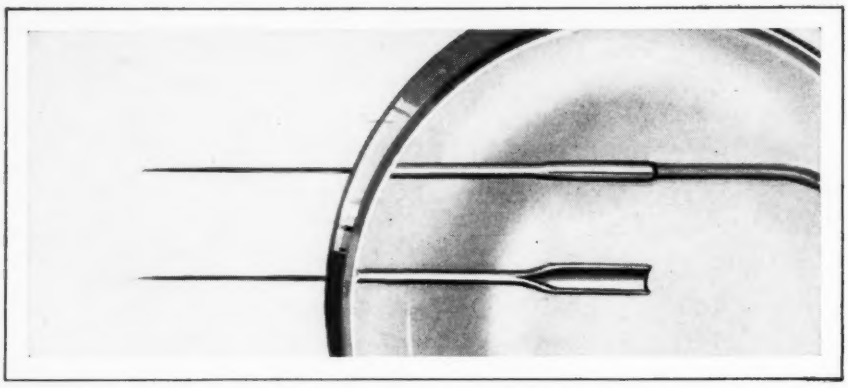
NEW YORK KANSAS CITY SAN FRANCISCO WINDSOR, ONTARIO

FACTS ABOUT STEARNS VITAMINS

EACH BIOMINES CAPSULE (Multiple Vitamins) CONTAINS: Vitamin A (Fish Liver Oils) 5000 U.S.P. Units; Vitamin D (Synthetic) 800 U.S.P. Units, Thiamine Hydrochloride (B_1) 2.0 mg., Riboflavin (B_2) 3.0 mg., Niacinamide 25.0 mg.; Ascorbic Acid (C) 75.0 mg.; Liver Concentrate (1:20) 80 mg. *Available in bottles of 25 and 100.*

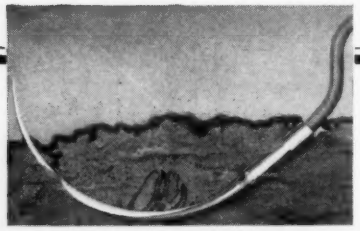
EACH VITAMIN B COMPLEX CAPSULE CONTAINS: Thiamine Hydrochloride (B_1) 2.0 mg., Riboflavin (B_2) 3.0 mg., Calcium Pantothenate 1.0 mg., Niacinamide 20.0 mg., Pyridoxine Hydrochloride (B_6) 0.1 mg., Liver Concentrate (1:20) 100 mg. *Available in bottles of 25, 100 and 250.*

TRADE-MARK BIOMINES – REG. U. S. PAT. OFF.



Avoid Excessive Suture Trauma

with **SCANLAN NEEDLED SUTURES**



Smooth union of suture and swaged-on-needle (upper illustration) avoids excessive tissue trauma caused by doubling of strand in needle eye (lower illustration).

• Various types of Scanlan suture materials are available with needles swaged to the suture strands. Such needled sutures are particularly advantageous for obstetrical, cervix, gastro-intestinal, skin, eye, and certain other types of specialized surgery.

The needles used on Scanlan sutures are of the highest grade needle steels. The magnified section illustrated above shows the open channel at the eye end of the needle and the smooth level union of suture and needle after the metal is firmly closed around the suture strand.

Send for illustrated literature describing Scanlan sutures for every surgical purpose. Also catalogs of delivery room and infant equipment, surgical tables and lights, SterilBrite furniture.

SCANLAN·MORRIS

Division of THE OHIO CHEMICAL & MFG. CO.

MADISON 4, WISCONSIN, U. S. A.

Manufacturers of

Sterilizing Apparatus
Operating Tables
Operay Surgical Lights
Scanlan Sutures

NOW AVAILABLE THROUGH
PRESCRIPTION PHARMACIES

SPECIFY

Penicillin, Abbott

PENICILLIN, ABBOTT
Supplied in rubber-stoppered, aluminum-sealed vials each containing 100,000 Oxford units

COMBINATION PACKAGE
Vial of 100,000 Oxford units of Penicillin; vial of 20-cc. Isotonic Solution Sodium Chloride, U.S.P.

ABBOTT LABORATORIES, NORTH CHICAGO • ILLINOIS

A Leader in Penicillin Research and Production

★ IODINE...A PREFERRED ANTISEPTIC ★

Its Toxicity is Low

The human leucocyte cell withstands a concentration of 1:600 iodine before its resistance is overcome. Leucocytic activity was found to be inhibited at much lower concentrations by other tested germicides.*

The low toxicity of Iodine in relation to its bactericidal action, is one of several reasons for its preference in surgery, in first aid... wherever an antiseptic for general use is needed.

*Welch, Henry, and Hunter, Albert C., Method for Determining the Effect of Chemical Antisepsis on Phagocytosis, Am. Jnl. of Public Health, Vol. 30, No. 2, Feb. 1940.

IODINE
Foe of Infection

Iodine Educational Bureau, Inc.
120 Broadway, New York 5, N. Y.

★ ★

Watson's

HERNIA

Featuring the Injection Treatment

by **LEIGH F. WATSON, M.D.**, Member of Attending Staff of California Lutheran Hospital and Methodist Hospital at Southern California, Los Angeles. 2nd Ed. 591 pages, 281 illustrations. Price, $7.50.

Hernia is an important surgical problem. There is more to it than a single method of treatment. To know about this condition you must be informed on all factors entering into its cause, what hernia involves, and the various methods for successfully treating each individual case. This information is given in the Second Edition of Watson's "Hernia." The coverage is complete—from Embryology to Legal Complications.

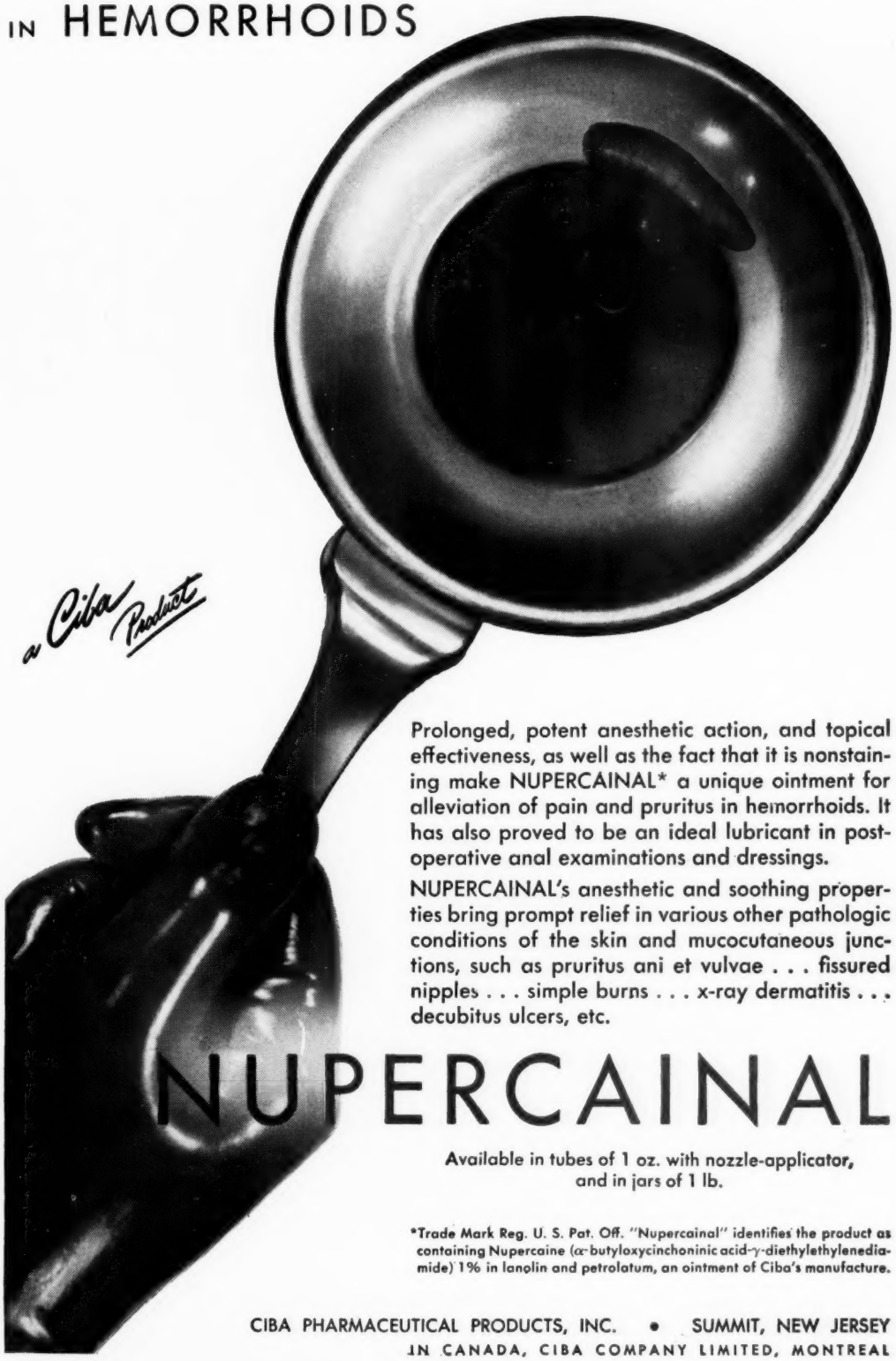
Every method of treatment—surgical and otherwise—is given, with special emphasis on Injection Treatment. Starting with an interesting historical introduction, the author considers the various types of hernias, local anesthesia in hernia operations, and the numerous operative procedures that experience has proved to be the best.

Illustrations are used profusely, making it easier to follow the suggested procedures. The anatomical details have been combined with the operative technique in the same drawings, thus greatly increasing the value of the illustrations. In all there are 281 illustrations.

Watson's "Hernia" is a well thought out and timely text, based on years of experience. Thanks to a great amount of clinical work and close observation this second edition offers you valuable help for the successful handling of your hernia problems.

The C. V. Mosby Company
Medical Publishers
St. Louis 3, Mo.

FOR RELIEF OF PAIN AND ITCHING IN HEMORRHOIDS



a Ciba Product

Prolonged, potent anesthetic action, and topical effectiveness, as well as the fact that it is nonstaining make NUPERCAINAL* a unique ointment for alleviation of pain and pruritus in hemorrhoids. It has also proved to be an ideal lubricant in postoperative anal examinations and dressings.

NUPERCAINAL's anesthetic and soothing properties bring prompt relief in various other pathologic conditions of the skin and mucocutaneous junctions, such as pruritus ani et vulvae . . . fissured nipples . . . simple burns . . . x-ray dermatitis . . . decubitus ulcers, etc.

NUPERCAINAL

Available in tubes of 1 oz. with nozzle-applicator, and in jars of 1 lb.

*Trade Mark Reg. U. S. Pat. Off. "Nupercainal" identifies the product as containing Nupercaine (α-butyloxycinchoninic acid-γ-diethylethylenediamide) 1% in lanolin and petrolatum, an ointment of Ciba's manufacture.

CIBA PHARMACEUTICAL PRODUCTS, INC. • SUMMIT, NEW JERSEY
IN CANADA, CIBA COMPANY LIMITED, MONTREAL

LIPPINCOTT SELECTED PROFESSIONAL BOOKS

Two Important Fields of Science Drawn Closer in

This New Book

PATHOLOGY in SURGERY

By NATHAN CHANDLER FOOT, M.D.

The role of pathology in surgery is presented by Dr. Foot in a fresh, crisp approach to this specialty. Here is a thorough coverage of the work of the pathologist and of the surgeon and their intimate relationships . . . carried through the operating room and the surgical ward, and the pathologist's laboratory.

PATHOLOGY IN SURGERY gives the pathologist, the surgeon, the internist or senior student the important perspective of dealing with living material . . . and the future of the patient rather than his past. What will probably happen to the patient as a result of any given lesion is presented in constructive, readable form. The material is planned to provide the surgeon with confirmation in making decisions affecting post-operative conditions.

The 21 chapters cover: Inflammation, Healing of Surgical Wounds, General Remarks on Tumors, Connective Tissues, Serous Membranes, Cardiovascular System, Blood-forming Organs, Respiratory System, Surgical Pathology of the Alimentary Tract, Liver, Gallbladder, and Pancreas, The Urinary System, Organs of Internal Secretion, The Breast, the Nervous System, the Male and Female Reproductive Systems, the Skin, Bone and Cartilage, and Lymphoid Tissue.

Richly illustrated in color and black and white—practically every illustration is original with this book and everyone has been selected for its value in illustrating the subject.

600 Pages—400 Illustrations—Tentative Price $10.00

A LIPPINCOTT SELECTED PROFESSIONAL BOOK — DROIT ET AVANT

J. B. LIPPINCOTT COMPANY, E. Washington Square, Philadelphia 5, Pa. S-5-45

Enter my order and send me: Pathology in Surgery, by Foot $10.00

☐ Charge my account ☐ Send C.O.D.

SEND TO: NAME .....

STREET ADDRESS .....

CITY, ZONE, STATE .....

Under your guarantee I will return book within 10 days, otherwise I will pay in full within 30 days.

LIPPINCOTT SELECTED PROFESSIONAL BOOKS

The fastest growing new suture material in Surgical History

● Now available in plentiful supply for civilian use, Ethicon Tantalum Sutures are being used in a wide variety of closures as surgeons become familiar with the handling qualities of this new metallic element.

Investigators report tantalum to be inert, non-corrosive and non-electroactive. It produces minimal tissue reaction. It has high tensile strength, exceptional malleability and is impermeable.

Ethicon Tantalum Sutures are used and tied in same manner as other non-absorbable sutures. Sizes 6-0, 5-0, 4-0, swaged to stainless steel eyeless Atraloc needles.

ORDER FROM YOUR SURGICAL DEALER

ETHICON *Sutures*

ETHICON SUTURE LABORATORIES

DIVISION OF JOHNSON & JOHNSON, NEW BRUNSWICK, N. J.

SELECT YOUR SULFONAMIDES AS YOU WOULD A SCALPEL

It is axiomatic that good surgery requires good tools —tools that fit the job at hand. It is no less important to select the proper sulfonamide in an appropriate dosage form to meet and deal most effectively with specific infections.

Sulfonamides, Lilly, for systemic and local administration, are provided in a complete variety of dosage forms for every indication. They are quickly available through the drug trade.
Eli Lilly and Company, Indianapolis 6, Indiana, U. S. A.

☆

SURGERY

VOL. 17 MAY, 1945 NO. 5

Original Communications

Symposium on the Ulcer Problem

A DIRECT VISUAL TECHNIQUE FOR STUDYING CHEMICAL AND OTHER INJURY TO EXPOSED MUCOSAL SURFACES

FRED KOLOUCH, JR., M.D.,* MINNEAPOLIS, MINN.

(From the Department of Surgery, University of Minnesota Hospitals)

MOST of the techniques devised to study the enzymatic hydrolytic effects of gastric juice upon the mucosa of the alimentary tract have failed to provide means of studying the early and the progressive effects of such chemical injury. The technique herein described is directed at assaying the early effects of such injury. The accessibility of the exteriorized segment to direct vision and continued inspection provides a satisfactory means of studying the chemical injury attending the dripping of various solutions upon such exteriorized segments.

METHOD

Pedicled segments of the gastrointestinal tract are brought out and exteriorized upon the anterior abdominal wall of dogs. The reactions of these mucosal grafts to the constituents of gastric juice, interference with circulation, or trauma of any nature may be observed directly and dynamically. Serial photographs and biopsies of observed anatomic changes may be obtained. Two objections to the technique are alteration of the environment of the intestinal mucosa and the exposure of the mucosa to trauma other than that employed in the experiments. Acute experiments performed on freshly exteriorized segments eliminate largely the latter disadvantage. Experiments of four to twelve hours' duration have been employed to study the immediate and early effects of gastric juice dripped on intestinal mucosa. When the observation of the late effects of this chemical trauma is to be observed, a permanent pedicled flap graft of intestinal mucosa is employed.

TECHNIQUE OF PREPARING THE EXTERIORIZED SEGMENT

Under intravenous sodium pentobarbital anesthesia, employing 15 mg. per pound of dog, using strict surgical technique, a laparotomy is performed through a midline incision. The desired segment of gut is located. A loop with a good blood supply is chosen and it is divided at

Received for publication, Nov. 20, 1944.

*Fellow of the National Cancer Institute, Bethesda, Md.

two points, four or five inches apart, between hemostatic forceps. The mesentery is divided down to its base in the nearest avascular areas below the two points of division, care being observed to protect the blood vessels to the isolated segment. In the acute experiments the open ends of the intestine are ligated with a heavy ligature. The isolated loop with blood supply intact is brought out upon the abdominal wall. The skin is loosely sutured around the pedicle, care being taken to avoid interference with the blood supply. The exteriorized intestinal segment is opened along the antimesenteric border and the corners are anchored to the skin of the abdominal wall by means of sutures. If protracted observations are to be carried out, one must re-establish the continuity of the intestine by means of an aseptic end-to-end anastomosis made over appropriate clamps. The isolated pedicled loop with blood supply intact is brought out through the skin incision and is opened along the antimesenteric border. A defect equal in area to the size of the opened bowel segment is made in the skin surrounding the laparotomy incision. Hemostasis is secured. The bowel segment is then sutured in the skin defect forming a pedicled flap graft of intestinal mucosa in the anterior abdominal wall of the dog. Sulfanilamide is spread over the site of anastomosis between the gut segment and the abdominal wall.

Employing this technique, it has been possible to exteriorize segments from all divisions of the gastrointestinal tract. However, due to the shortness of the common bile duct in the dog, it has been difficult to exteriorize the gastric antrum and the first portion of the duodenum. However, if the common bile duct is ligated and divided, these segments can be brought out. For acute experiments, no effort is made to re-establish re-entry of the bile into the intestinal canal. For protracted observations, a cholecystoenterostomy may be performed.

With a slight modification of technique, a preparation may be made in which vascular phenomena can be studied. The mesentery of the gut is pulled over to one side and tacked between the skin and the edge of the opened intestine. The arteries subsequently may be dissected out, and the effects of emboli or medicaments injected through a fine caliber needle may be noted.

The reactions of these mucosal segments are studied as follows: The dogs being anesthetized are secured to a wooden frame in the supine position. The experimental solutions are then dripped on the mucosa and the reactions observed as they progress. The tissue may be photographed and biopsies may be taken at any time.

This method of studying the effects on isolated exteriorized segments of gastric juice, obtained from dogs with isolated pouches under histamine stimulation as well as hydrochloric acid with or without the addition of pepsin, dripped at a constant rate upon the exteriorized segment suggest definitely that all segments of the gastrointestinal canal are susceptible of injury by this means with 0.1 normal hydrochloric acid. The importance of pepsin in augmenting the injury produced by hydrochloric acid is obvious, as is also the effect of trauma to the exteriorized mucosa.

Fig. 1 demonstrates the progressive damage to duodenal and antral mucosa produced by dripping on an isotonic acid solution of pH 1.2

at one point on both the antrum and the duodenum and acid gastric juice (pH 1.12) obtained from a histamine-stimulated Heidenhain pouch on another for a period of three and one-half hours. The enhancement of degree of mucosal destruction by trauma induced by gently stroking

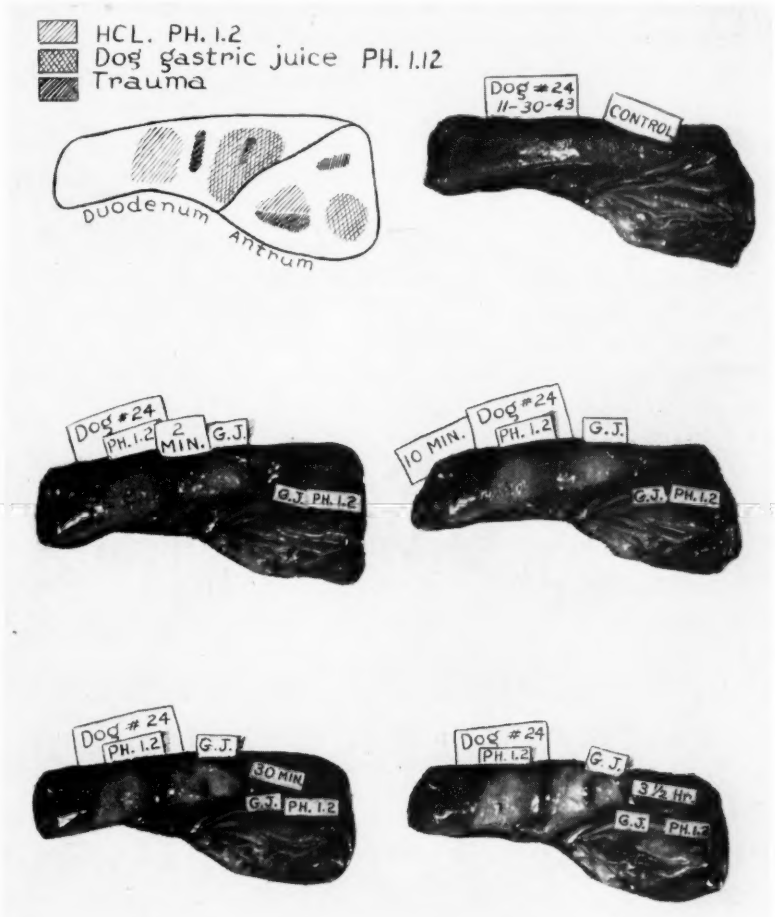


Fig. 1.—Experimental Dog 24. Photographic series revealing chronologically the alterations in exteriorized gastric antral and duodenal mucosa of a dog exposed to an isotonic hydrochloric acid solution of pH 1.2 and to dogs' gastric juice of pH 1.12 obtained from histamine-stimulated Heidenhain pouches. The effect of trauma in the normal mucosa and that damaged by the gastric juice induced by stroking it every five minutes with the rubber eraser of a pencil is also shown.

A, Topographic map designating areas of antral and duodenal mucosa dripped with hydrochloric acid and gastric juice. The regions traumatized are also revealed.

B, Control reveals character of mucosa of the opened exteriorized gastric antrum and duodenum.

C, Alterations two minutes after dripping designated areas with the isotonic hydrochloric acid solution pH 1.2 and the dogs' gastric juice (pH 1.12). Antrum reveals no damage in either area. Duodenal mucosa has reacted in this short time to both solutions by marked edema and gray discoloration of the mucosa.

D, Alterations within ten minutes. Antral mucosa shows no effect. Duodenal mucosa has become increasingly edematous and a superficial gray exudate has appeared in both areas.

E, Alterations within thirty minutes. Antral mucosa still resists corrosive action of both gastric juice and the acid as well as trauma. The duodenal mucosa is markedly damaged with an increase in the intensity of the edema; exudate and now superficial necrosis is present at both regions but slightly greater in the area exposed to gastric juice. Trauma has caused a slight erythema barely perceptible in the photograph in the normal mucosa in contrast to erosion and small petechial hemorrhages in region exposed to gastric juice.

F, Alterations after three and one-half hours' exposure. The antral mucosa has resisted the acid solution of pH 1.2 as well as trauma alone. Spontaneous petechial hemorrhages occurred in region exposed to gastric juice after two hours and increased up to this point. Traumatization caused superficial erosion and increased the bleeding in the area damaged by gastric juice. The duodenal mucosa has been markedly damaged by both the acid and the gastric juice. The exudation and necrosis being more marked by the effects of the latter. Traumatization of the normal duodenal mucosa has caused increased erythema and some extravasation of blood in contrast to the excavated hemorrhagic ulcer in the region damaged by gastric juice.

the regions exposed to gastric juice is obvious. Duodenal damage consists of progressive edema and necrosis and commences within two minutes, progressing very rapidly in both exposed areas. The antral mucosa is much more resistant, as it shows no tendency to necrosis or ulceration in the area exposed to the acid or trauma alone. On the other hand, petechial hemorrhages occurred in the area exposed to gastric juice after two hours. Trauma caused ulceration and hemorrhage in the damaged duodenal mucosa and only hemorrhage in the damaged antral mucosa.

It is proposed to attempt to determine the susceptibility of various segments of the gastrointestinal canal to such chemical injury.

CONCLUSION

A method of studying the effects of chemical and other types of trauma to various segments of the gastrointestinal canal is described. The celerity with which evidences of mucosal injury appear, attending the dripping of solutions of hydrochloric acid within the physiologic range upon exteriorized segments ,is striking. The deleterious effect of local trauma is apparent.

THE PATHOGENESIS OF CAFFEINE-INDUCED ULCERS

J. A. Roth, M.B., Ph.D., and A. C. Ivy, Ph.D., M.D., Chicago, Ill.
(From the Department of Physiology, Northwestern University Medical School)

INTRODUCTION

THE observation of Judd[1] on the production of acute and subacute gastric ulcers in cats by the intramuscular implantation of caffeine in a beeswax-mineral oil mixture was recently confirmed by us.[2] A hypothetic analysis of the pathogenesis of the caffeine-induced ulcer was presented. Since then we have demonstrated that caffeine is a potent stimulus for the secretion of acid and pepsin.[3, 4] In addition it was noted that when histamine and caffeine were given alternately, acute bleeding erosions and ulcers could be observed to develop during a period of five or seven hours. This rendered it possible to study the pathologic histogenesis of these ulcers in considerable detail.

In this paper we shall report the vascular changes in the gastric mucosa produced by caffeine, and elaborate upon the other factors in the pathogenesis of caffeine-induced ulcer.

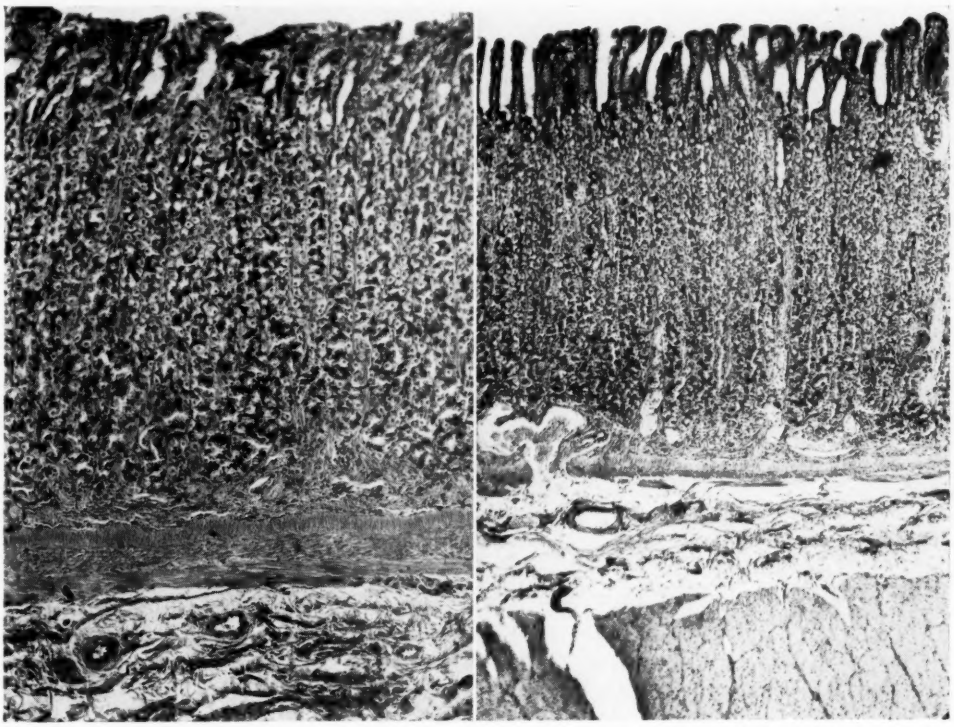
METHODS

In eight acute experiments with cats under light chloroform anesthesia, an incision was made through the serosa, muscularis, and mucosa of a relatively avascular area of the stomach. The mucosa everted, forming a stoma which was protected and kept moist by normal saline solution. After a control period of fifteen minutes during which time the

Received for publication, Sept. 5, 1944.

red intensity of the mucosa was estimated in comparison with a Tallqvist hemoglobin scale,[5] several small sections of the stomach wall were cut from the free edge and fixed immediately in formaldehyde for microscopic study. Then caffeine was slowly administered intravenously (250 mg. caffeine sodium benzoate), the intensity of redness was estimated, and sections of stomach wall were removed from an area adjacent to the control at fifteen-minute intervals for sixty to seventy-five minutes.

Control experiments were conducted using an equivalent amount of sodium benzoate (125 mg.) in an equal volume of physiologic saline solution (1 c.c.). Precautions were taken to keep manipulations of the stomach to a minimum. All of the animals were fasted ten to twelve hours previous to the experiments.



A. *B.*

Fig. 1.—Control. *A*, Photomicrograph of gastric mucosa before caffeine (×145). Note absence of vessels in the mucosa. *B*, Photomicrograph of gastric mucosa one hour after caffeine (×80). Note dilated and engorged venules in the mucosa and submucosa. Lower magnification was selected to show a larger field.

RESULTS

Direct observation of the gastric mucosal stoma in the cat showed a persistent reddening (hyperemia) after the intravenous administration of caffeine, followed in one hour by cyanosis. During the phase of hyperemia, the mucosa became thickened, moist, and succulent; the rugae became fuller and smoother. Kodachrome photography recorded these changes.

Fig. 1 shows the microscopic vascular changes following administration of caffeine. When the mucosa grossly appeared more reddened (an average change from 20 to 50 per cent on the Tallqvist scale), the veins and venules of the submucosa appeared markedly dilated and engorged with blood. However, when the mucosa appeared cyanotic there was

marked dilatation and engorgement of the mucosal venules, which previously were not apparent to any great extent, and scattered collections of serous transudate and extravasated blood elements were observed. These gross and microscopic vascular changes suggest the following train of events: vasodilatation and engorgement, vascular stasis, local anoxia, increased capillary permeability, transudation, extravasation of blood elements, and decreased cell nutrition.

The mucosa in the control experiments did not show any similar vascular changes.

DISCUSSION

The central and peripheral actions of caffeine on the blood vessels are antagonistic. Caffeine tends to constrict blood vessels by stimulation of the medullary vasomotor center, and to dilate them by a direct effect on vascular musculature.[6] Goodman and Gilman state that, "after therapeutic doses, the peripheral vasodilator action predominates. Oncometer studies in experimental animals show that there is a definite increase in organ volume following the administration of a xanthine." Early investigators reported an increased volume of the splanchnic and cerebral regions after stimulating doses of caffeine due to persistent vasodilatation.[7-9] The present studies upon the gross and microscopic vascular changes induced by caffeine confirm the vasodilatation as specifically related to the gastric mucosa. A discussion of some of the factors which appear to be involved in the pathgenesis of caffeine-induced ulcers in cats follows.

We have suggested[2] that the proteolytic action of acid and pepsin secretion upon a gastric mucosa, rendered more susceptible to the ulcerative process by the vascular and "cellular" changes induced by caffeine, results in the development of an ulcer.

Caffeine and its related beverages have been shown to be potent stimulants of *both* the acid and pepsin content of gastric juice in man and the cat.[3, 4, 10] Considerable evidence indicates that the excessive continuous secretion of gastric juice with relative or absolute deficient neutralization is one of the major factors in the pathogenesis of human gastroduodenal ulcers.[11] With this in mind and in order to produce ulcers experimentally, it was thought desirable to provoke the constant elaboration of gastric juice so that when the stomach was empty of food content a relative deficient neutralization would be obtained. Thus, in an attempt to obtain prolonged and continuous caffeine action, the technique of embedding caffeine in a beeswax-mineral oil mixture was used as in the experimental production of "histamine ulcers."[12, 13]

Attention is called to the fact that when the histamine mixture was implanted subcutaneously, infectious abscesses almost invariably developed at the site of injection.[14] It is conceivable that the decreased general resistance of the body that accompanies chronic infectious foci may play a contributory role in the pathogenesis of histamine-induced ulcers. It is a well-known clinical observation that recurrences of gastroduodenal ulcers are more frequent in the presence of focal infectious processes. However, it is unlikely that a similar factor is involved in the pathogenesis of "caffeine ulcers" inasmuch as no similar abscesses were observed when the caffeine mixture was implanted *intramuscularly*.

In recent years considerable emphasis has been placed upon the acid and pepsin factors, but opinion has been divided as to the relative importance of one over the other; hence the designations "peptic ulcer" and "acid ulcer." However, this is an artificial distinction since the proteolytic action of gastric juice is not due to acid or pepsin alone, but to pepsin in acid solution.[15]

The consensus today is that "ulcer of the stomach is in some way due to a *local loss of resistance* on the part of the mucous membrane to the digestant activity of the gastric juice."[11] This factor is too frequently overlooked in a consideration of the pathogenesis of spontaneous or experimentally induced ulcers; as a consequence, investigators have recently directed their attention and emphasis upon the importance of acid and/or pepsin to the exclusion of those *factors which increase the susceptibility of the mucosa* to the proteolytic action of acid and pepsin. Some of these factors with reference to caffeine will be discussed.

The microscopic picture suggests that the marked vasodilatation and engorgement might in turn give rise to stasis, increased capillary permeability, transudation, extravasation of formed blood elements, and impaired cell nutrition, all of which would contribute to the devitalization of the mucosa and the development of an ulcer. Babkin takes the position that the devitalizing mechanism is one of vasodilatation and stasis.[18] Direct observation of a mucosal stoma in the cat shows a persistent blushing (hyperemia) after the intravenous administration of caffeine, followed by cyanosis.

Vascular changes in the gastric mucosa similar to those induced by caffeine in the cat have been observed in man under various conditions. In their experiments upon a modern "Alexis St. Martin," Wolf and Wolff[5] observed that "intense anxiety, hostility and resentment were accompanied by severe and prolonged engorgement, hypermotility and hypersecretion in the stomach. In this state mucosal erosions and hemorrhages were readily induced by even the most trifling traumas and frequently bleeding points appeared spontaneously as the result of vigorous contractions of the stomach wall." Thus, a hyperemic succulent mucosa, whether provoked by emotional reactions or caffeine, is apparently "friable" and susceptible to the ulcerative process.

Continuous or repeated stimulation of gastric secretion in the anesthetized cat with histamine for ten to twelve hours produces no apparent change in the gastric mucosa.[2] But, if caffeine (250 mg. caffeine sodium benzoate, intravenously or by direct lavage of the stomach, for thirty minutes) is alternated with the histamine (0.3 mg.), large diffuse areas of epithelial desquamation, multiple bleeding erosions, and ulcerations of the gastric mucosa are observed in as short a time as five hours (Figs. 2 and 3). Since both caffeine and histamine stimulate the flow of an acid gastric juice and cause vasodilatation, and since histamine alone does not induce ulceration of the gastric mucosa in acute experiments, caffeine may provide an additional factor which contributes to the decreased resistance of the mucosa. This alteration in the susceptibility of the gastric mucosa to the proteolytic action of gastric juice has been arbitrarily designated and attributed to "cellular toxicity." This factor may involve alteration in cell permeability, the concept of caffeine-histamine synergism,[16] or a more prolonged stimulation of pepsin than

that provoked by histamine.[4] Schiffrin and Warren[15] have shown that the incidence of experimentally induced ulcerations of the gastrointestinal tract is much higher by perfusion, with optimum concentrations of acid and pepsin than by perfusion with acid alone. Thus, the vascular

Fig. 2.—Acute experiment, gastric contents were continuously drained out through a pyloric cannula. Sequence of gastric stimulations: 0.5 mg. histamine, subcutaneously 100 mg. caffeine (lavage for thirty minutes), and 0.5 mg. histamine, subcutaneously. Duration of experiment seven hours. Note diffuse areas of superficial desquamation of epithelium, multiple bleeding erosins, and ulcerations of the gastric mucosa.

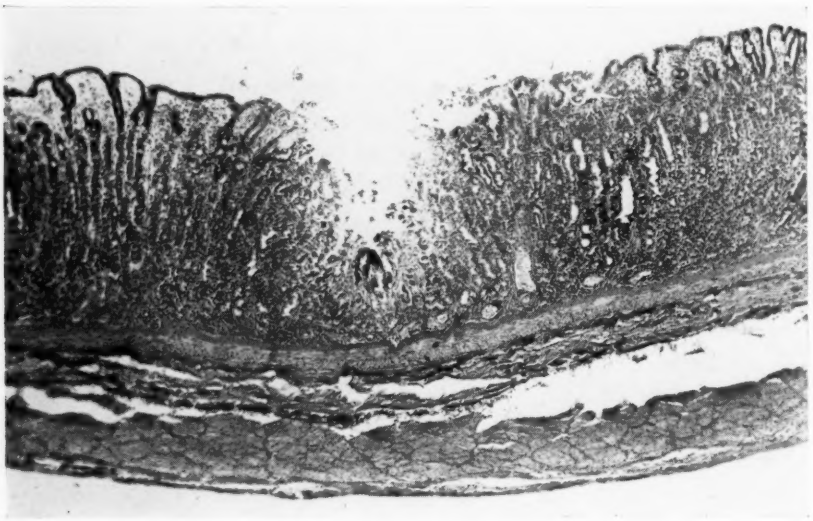


Fig. 3.—Photomicrograph of an acute erosion. Note superficial mucosal defect with fragmentation of the glandular epithelium, venule dilatation, engorgement, and thrombosed vessel.

changes and factor of "cellular toxicity" are implicated in the pathogenesis of caffeine-induced ulcers in cats by increasing the susceptibility of the mucosa to the digestive action of gastric juice.

In addition to the direct pharmacodynamic effects of caffeine upon the stomach, there may or may not be a *neurogenic factor* by virtue of the excitatory action of caffeine upon the central nervous system. It is a well-established clinical observation that the emotionally tense, con-

scientious, hard-working individuals generally constitute the ulcer diathesis. Also, prolonged resentment, hostility, and anxiety are commonly associated with recurrence or perpetuation of an ulcer. It is conceivable that the consumption of large quantities of caffeine-containing beverages might aggravate these neurogenic factors and thus contribute to a vicious cycle in their influence upon human gastroduodenal ulcers.

We have previously noted the species difference in the secretory response to caffeine;[2] gastric secretion is stimulated in man and in the cat, but not in the dog. An attempt was also made to produce ulcers in dogs by the intramuscular implantation of caffeine in beeswax and mineral oil, but no change was observed in the gastric or duodenal mucosa after daily injections over a period of three months. The explanation for this species difference is not apparent at present. The gastric mucosa of the cat appears to be more susceptible to ulceration than the duodenal mucosa; the incidence of "histamine ulcers" as well as "caffeine ulcers" in the gastric mucosa outnumbers those in the duodenal mucosa of the cat.[1, 2, 13] The converse is true of the location of histamine-induced ulcers in the dog.[13]

Ivy[17] concluded that, "if those reported failures of atropine, in doses adequate to cause complete xerostomia and disturbances of vision, to abolish the gastric secretory response to a meal in man are not due to the presence of an ulcer or a 'pre-ulcer' condition, then normal men have a gastric secretory mechanism not found in the normal dog." It is evident from the present studies on caffeine that normal man does possess a gastric secretory mechanism not found in the normal dog.

SUMMARY

Evidence is presented in support of some of the factors which appear to be involved in the pathogenesis of caffeine-induced ulcers. It is believed that the proteolytic action of acid and pepsin secretion upon a gastric mucosa, rendered more susceptible to the ulcerative process by the vascular and "cellular" changes induced by caffeine, results in the development of an ulcer.

REFERENCES

1. Judd, E. S., Jr.: Bull. Am. Coll. Surgeons **28**: 46, 1943.
2. Roth, J. A., and Ivy, A. C.: Gastroenterology **2**: 274, 1944.
3. Roth, J. A., and Ivy, A. C.: Am. J. Physiol. **141**: 454, 1944.
4. Grossman, M. I., Roth, J. A., and Ivy, A. C.: Gastroenterology. (In press.)
5. Wolf, S., and Wolff, H.: Human Gastric Function, New York, 1943, Oxford University Press, J. A. M. A. **120**: 670, 1942.
6. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, 1941, The Macmillan Company, p. 277.
7. Phillips, J., and Bradford, J. R.: J. Physiol. **8**: 117, 1887.
8. Gottlieb, R., and Magnus, R.: Arch. f. exper. Path. u. Pharmakol. **45**: 223-248, 1901.
9. Loewi, O.: Sitzungsb. Marburg, July, 1904.
10. Roth, J. A., Ivy, A. C., and Atkinson, A. J.: J. A. M. A. **126**: 814, 1944.
11. Dragstedt, L.: Arch. Surg. **44**: 438, 1942.
12. Walpole, S. H., Varco, R. L., Code, C. F., and Wangensteen, O. H.: Proc. Soc. Exper. Biol. & Med. **44**: 619, 1940.
13. Hay, L. J., Varco, R. L., Code, C. F., and Wangensteen, O. H.: Surg., Gynec. & Obst. **75**: 170, 1942.
14. Shoch, D., and Grossman, M. I.: Personal communication.
15. Schiffrin, M. J., and Warren, A. A.: Am. J. Digest. Dis. **9**: 205, 1942.
16. Roth, J. A., and Ivy, A. C.: Am. J. Physiol. **142**: 107, 1944.
17. Ivy, A. C.: SURGERY **10**: 861, 1941.
18. Babkin, B. P.: Canad. M. A. J. **38**: 421, 1938.

INFLUENCE OF CAFFEINE ON ULCER GENESIS

Experimental Production of Gastric Ulcer in Guinea Pigs and Cats With Caffeine, Together With a Study of Its Effect Upon Gastric Secretions in Dog and Man

K. Alvin Merendino, M.D.,* Edward S. Judd, M.D., Ivan Baronofsky, M.D., Sidney S. Litow, M.D., Bernard G. Lannin, M.D., and Owen H. Wangensteen, M.D., Minneapolis, Minn.

(From the Department of Surgery, University of Minnesota)

INTRODUCTION

MAN appears to be "addicted" to various beverages containing methyl derivatives of xanthine. The most important ones are caffeine (trimethylxanthine), the principal alkaloid of coffee, tea, kola, etc., and theobromine from cacao. Certain popular soft drinks also contain substantial amounts of caffeine. A strong cup of coffee or tea contains 0.10 to 0.12 Gm. of caffeine. The well-known pharmacologic action of these drugs is essentially that of the alkaloid present.[1,2]

Because of (1) the widespread use of caffeine-containing beverages, (2) the limited tolerance of habitual consumers of caffeine, (3) the general acceptance of the doctrine that coffee and tea should be eliminated from the diet of the ulcer patient, and (4) the apparent confusion in the literature regarding the effect of caffeine on gastric secretion, it was suggested that a further evaluation of this problem should be made.

A few years ago (1940), the possible relationship of caffeine upon gastric secretion was brought to light in a rather striking manner. A young man was admitted to hospital with a perforated "peptic" ulcer. He gave a history of having ingested approximately 150 bottles of an iced kola drink over a period of five days during the heat of August. He gave no antecedent story of ulcer. Later, another patient presented himself experiencing extreme difficulty with a doudenal ulcer. A careful review of his habits revealed that he was a self-styled coca-cola "addict." In this latter case, the association of these two conditions may have been coincidental. However, in the first patient, it is difficult to set aside the possibility of a causal relationship. It was the observation of these two cases that suggested subjecting the caffeine influence in ulcer genesis to experimental scrutiny. A preliminary report was made from this clinic on the matter by Judd[6] in 1942.

PREVIOUS STUDIES

In a review of the American and English literature, little work of primary importance has been done.

Allard[1] (1904) discovered at autopsy gastric hemorrhages and erosions in patients receiving Theocin, a proprietary name for synthetic theophylline having the same pharmacologic action as caffeine. Experimentally, in dogs he administered theocin by nasal tube. The dosage

The researches presented here were supported by grants of the Augustus L. Searle Fund for Experimental Surgical Research, the Citizens Aid Society, and the Zimmerman Fund for Surgical Research.

*Trainee of the National Cancer Institute, Bethesda, Md.

varied from 0.29 to 0.76 Gm. per kilogram of body weight. In three to eleven days he noticed gastric hemorrhages and erosions; rabbits developed bleeding areas, cats only edema of the mucosa.

In 1906, Pincussohn[8] observed a prompt rise in the free and total acid, as well as volume of gastric juice in dogs with Pavlov pouches given 300 c.c. of a coffee mixture containing 20 Gm. of coffee. Using cocoa, which contained only 15 per cent of its normal fat content, a slight increase in gastric acidity was evident. Tea (10 Gm. in 300 c.c. of water) was observed to decrease the pouch secretion.

Salant and Rieger[11] (1909) administered caffeine subcutaneously to dogs. Eleven centigrams were sufficient to kill the experimental animals. At autopsy "inflammation and ulceration of the intestines and especially of the stomach" were present.

In 1933 and 1934, Hanke[3, 4, 5] was able to produce erosions in the esophagus, stomach, and duodenum using large hypodermic injections of caffeine in cats. He called these "immediate peptic ulcers." Subsequently, Hanke observed "chronic peptic ulcers" with caffeine by the daily subcutaneous injection of 200 to 300 mg. of caffeine sodiosalicylate. These ulcers were superimposed upon a severe gastritis. He noted that caffeine caused a sharp increase in the degree of gastric acidity and volume. He concluded that he was dealing with a "primary peptic gastritis occurring in a highly acid gastric juice. This powerful secretion leads to erosion."

Molteni,[7] in 1938, noted ulcerative lesions in the rat when injected daily with 10 to 25 eg. of caffeine sodiosalicylate. When given smaller doses over a period of seventy days, 40 per cent of twenty-four rats developed ulcers. These lesions appeared in the antrum and pylorus. Molteni felt that the hyperacidity of the gastric juice was the principal, but not the only factor involved.

The studies reported herewith represent an amplification of the preliminary report of Judd[6] (1942), the writing and publication of which work was suspended by the exigencies of the war.

Recently, Roth and Ivy[9, 10] (1944) reported upon the effects of caffeine upon the gastric secretions in the dog, cat, and man. Caffeine sodium benzoate, 65 to 250 mg., was given by various routes. These investigators concluded that: (1) caffeine does not stimulate gastric secretion in the dog, (2) caffeine administered by the intravenous route or by lavage of the stomach provokes a copious flow of acid gastric juice in the cat, and (3) caffeine administered intramuscularly or orally stimulates gastric secretion in man.

METHODS OF STUDY AND RESULTS

I. *The Production of Ulcers in Guinea Pigs and Cats.*—First, a series of five guinea pigs was used. Daily, each experimental animal was injected intramuscularly with 200 mg. of caffeine alkaloid in beeswax. The preparation was in accord with the method described by Code and Varco[2] for histamine in beeswax. Caffeine was substituted for histamine in their formula. The caffeine alkaloid in beeswax mixture was prepared freshly each day.

After the initial injection, the guinea pigs became lethargic, anorexic, and, in short, exhibited a severely toxic state. None of these animals survived the fifth injection (see Table I).

TABLE I

GUINEA PIGS

NO.	SURVIVAL DAYS	AUTOPSY RESULTS
1	3	Negative
2	3	Negative
3	5	Negative
4	3	Negative
5	4	Mild gastritis; moderate duodenitis

Dosage: 200 mg. of caffeine alkaloid in beeswax intramuscularly daily.
Average weight: 976 Gm.

Only one of the guinea pigs (Pig 5) showed any suggestive gastric pathology. Because of the drug toxicity in the dosage given and the short survival period, the results obtained are of little or no value. Consequently, the dosage was reduced. A series of ten guinea pigs was used. Daily these animals were injected intramuscularly with 100 mg. of caffeine alkaloid in beeswax. This mixture was prepared as previously described (see Table II).

TABLE II

GUINEA PIGS

NO.	SURVIVAL DAYS	AUTOPSY RESULTS
1	1	Negative
2	3	Shallow erosion 3 mm. in diameter; 8 mm. distal to pylorus
3	5	Shallow erosion in the fundus 3 mm. in diameter; a duodenal ulcer 3 mm. in diameter, 4 mm. distal to the pylorus
4	5	Multiple shallow hemorrhagic ulcers throughout the stomach but particularly in the corpus
5	7	Negative
6	10	3 small mucosal hemorrhages in the corpus; no ulcer
7	5	Shallow erosion in the pylorus
8	7	Multiple small mucosal antral hemorrhages; no ulcer
9	10	One small submucosal hemorrhage in the corpus; no ulcer
10	10	One small submucosal antral hemorrhage; no ulcer

Dosage: 100 mg. of caffeine alkaloid in beeswax intramuscularly daily.
Average weight: 890 Gm.

The survival time was prolonged somewhat and the incidence of gastroduodenal pathology was increased markedly. Eight of the ten guinea pigs (80 per cent) exhibited upper gastrointestinal pathology. These changes varied from small mucosal hemorrhages to definite ulcer production. Four of the guinea pigs (40 per cent) developed erosions or ulcers (see Fig. 1).

Next, a series of twenty-six cats similarly was injected daily with 300 mg. of caffeine alkaloid in beeswax. All injections were made intramuscularly. These animals tolerated the drug fairly well. Some hyperactivity and excitement were noted after the initial injections; however, terminally, a state of lethargy ensued. Fourteen of the twenty-six cats (53.9 per cent) exhibited gastric and/or duodenal pathology (see Table III).

Nine cats developed ulcers. These ulcers were punched out, sharply defined, and in several instances multiple lesions were present. The

lesions were similar in all respects to the "peptic" ulcers found in man (see Fig. 2).

II. *Studies on Dogs With Gastric Pouches.*—Desirous of establishing the effect of caffeine on gastric secretions, pouch dogs were injected subcutaneously with various doses of freshly prepared solutions of aqueous caffeine citrate and aqueous caffeine alkaloid. Both drugs are 50 per cent solutions of caffeine.

These pouch dogs had been standardized, fasting for five consecutive hours on three separate occasions. In this manner, a mean standard fasting curve was established for each animal. Routinely, food pans were removed seventeen hours prior to experiments, although water was allowed the dogs up until but not during the testing period. All dogs were given one or more days' rest between experiments. Identical diets were maintained on regular feeding schedules during the resting days.

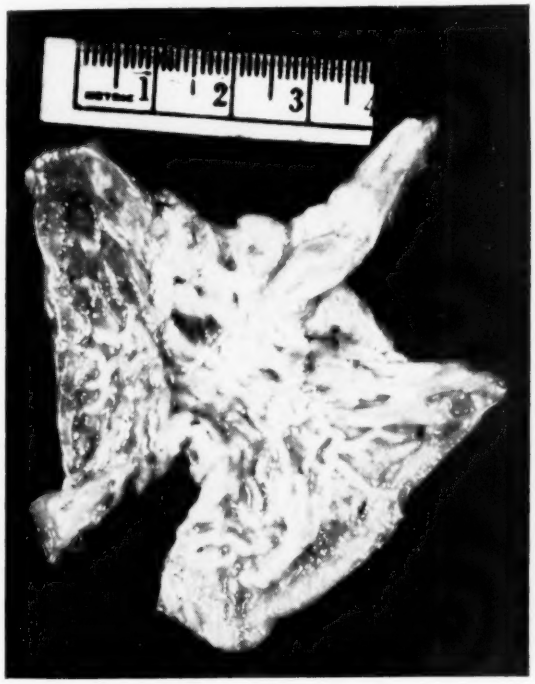


Fig. 1.

Fig. 2.

Fig. 1.—Guinea pig 4, Table II. Multiple shallow hemorrhagic ulcers were produced in the guinea pig throughout the entire stomach attending the daily intramuscular injection of 100 mg. of crude caffeine alkaloid in beeswax for five days.

Fig. 2.—Cat 24, Table III. This experimental animal was injected intramuscularly daily for twelve days with 300 mg. of crude caffeine alkaloid in beeswax. Several hemorrhagic erosions were present in the corpus of the stomach. The antrum revealed two punched out ulcers. In the duodenum, submucosal hemorrhages were observed.

In these experiments, pouch juice was collected under similar conditions for one hour, from 9 to 10 A.M., and this was used as the fasting sample for that experiment. Freshly prepared aqueous caffeine alkaloid (300 to 1,200 mg.) was injected subcutaneously. Subsequent hourly samples were collected in clean test tubes. No attempt was made to correlate dosage with body weight.

At the conclusion of the experiment, each hourly sample was titrated with 0.1 NaOH, using Toepfer's solution and phenolphthalein as indicators for free and total acid. Volumes were measured to .1 centimeter.

TABLE III

CATS

NO.	SURVIVAL DAYS	AUTOPSY RESULTS
1	23	Antral ulcer; duodenal ulcer
2	3	Linear antral ulcer
3	15	Negative
10	4	Negative
11	16	Multiple small hemorrhages in the fundus; 2 antral ulcers (4 mm.; 3 mm.)
12	22	3 linear antral erosions
13	24	Multiple long, deep linear ulcers in the corpus; 2 antral ulcers
14	28	Negative
15	4	Negative
16	14	Scattered duodenal petechiae; no ulcer
17	9	Negative
18	5	Negative
19	10	3 mm. shallow hemorrhagic antral ulcer; 2 tiny erosions about the ulcer
20	15	Negative
21	11	Multiple pinhead submucosal duodenal hemorrhages
22	6	Negative
23	19	3 irregular submucosal hemorrhages in the antrum
24	12	2 punched out antral ulcers (4 mm.; 5 mm.). Multiple small erosions in the corpus; submucosal duodenal hemorrhages
25	15	Negative
26	9	Severe hemorrhagic gastritis and scattered erosions in the corpus
27	11	Negative
28	8	Prepyloric ulcer
29	1	Negative
30	11	Multiple gastric ulcers; moderate gastritis
31	10	Antral ulcer; antral erosion
32	1	Negative

Dosage: 300 mg. of caffeine alkaloid in beeswax intramuscularly daily.
Average cat weight: 6.3 pounds.

Twenty-two experiments were performed on nine pouch dogs. A difference of 20 degrees of free acid between the dogs' fasting sample and the free acid during the subsequent four hours was arbitrarily chosen as our criterion for a stimulation or depression effect. In some experiments, the variation of free acid was less than plus or minus 20 degrees from the dogs' fasting free acid level. Such an occurrence was considered as not being a significant change. In other experiments, the dogs' fasting free acid level was 0 degrees and remained so throughout the procedure. In this last type of result, one can state only that no stimulating effect occurred; obviously, a depressant effect cannot be excluded.

TABLE IV

HEIDENHAIN AND PAVLOV POUCH DOGS—THE EFFECT OF AQUEOUS CAFFEINE CITRATE ON POUCH SECRETIONS

NO.	WEIGHT (LB.)	DOSE OF CAFFEINE (MG.)	ROUTE	EFFECT
117 P	34	150	Subcutaneously	Fasting at 0, and remained 0
20 H	49	300	Subcutaneously	Depression
9 H	42	300	Subcutaneously	Fasting at 0, and remained 0
20 H	49	300	Subcutaneously	Fasting at 0, and remained 0
132 H	45	600	Subcutaneously	Depression
116 P	40	600	Subcutaneously	No significant change

H—Heidenhain pouch dog.
P—Pavlov pouch dog.

In most of these experiments, no significant changes in the volume of the pouch secretions were noted. Aqueous caffeine citrate in dosages of 150, 300, and 600 mg. was injected subcutaneously in six experiments (see Table IV). No stimulation effect on gastric acidity was noted in any instance.

Using comparable dosages of aqueous caffeine alkaloid, somewhat similar results were noted. However, when dosages of 1,200 mg. of aqueous caffeine alkaloid were injected subcutaneously, a stimulation effect of pouch acidity was observed in four of six experiments (66⅔ per cent). It usually occurred during the third and fourth hour after the administration of the drug. No toxic symptoms were noted in any instance with this dosage. No important differential response in pouch secretions was noted between the Heidenhain (vagus destroyed) and Pavlov (vagus intact) pouch dogs (see Table V *A*).

TABLE V *A*

HEIDENHAIN AND PAVLOV POUCH DOGS—THE EFFECT OF AQUEOUS CAFFEINE ALKALOID ON POUCH SECRETIONS

NO.	WEIGHT (LB.)	DOSE (MG.)	ROUTE	EFFECT
11 P	43	300	Subcutaneously	Fasting at 0, and remained at 0
15 P	56	300	Subcutaneously	Stimulation
116 P	40	600	Subcutaneously	No significant change
128 H	42	600	Subcutaneously	Depression
18 P	48	600	Subcutaneously	No significant change
117 P	46	600	Subcutaneously	No significant change
16 P	69	600	Subcutaneously	Fasting at 0, remained 0 throughout
125 P	54	600	Subcutaneously	Fasting at 0, remained 0 throughout
9 H	42	600	Subcutaneously	Depression
129 H	52	600	Subcutaneously	Stimulation
20 H	49	1,200	Subcutaneously	Stimulation
18 P	48	1,200	Subcutaneously	Stimulation
11 P	43	1,200	Subcutaneously	Fasting at 0, remained at 0
20 H	49	1,200	Subcutaneously	Stimulation
132 H	45	1,200	Subcutaneously	Stimulation
132 H	45	1,200	Subcutaneously	Depression

TABLE V *B*

THE EFFECT OF CAFFEINE ALKALOID IN BEESWAX ON POUCH SECRETIONS

NO.	DOSE (MG.)	ROUTE	EFFECT
44 H	2,500	Injected daily for 4 consecutive days intramuscularly	Stimulation
16 P	2,500	Injected daily for 4 consecutive days intramuscularly	Stimulation
20 H	2,500	Injected daily for 4 consecutive days intramuscularly	Stimulation
11 P	2,500	Injected daily for 4 consecutive days intramuscularly	Stimulation
254 P*	2,500	Injected daily for 4 consecutive days intramuscularly	Stimulation
289 P	2,500	Injected daily for 4 consecutive days intramuscularly	Stimulation

*This experimental animal was subjected to the same experiment on two occasions. In one experiment caffeine sodium benzoate was substituted for the caffeine alkaloid. The results were the same.

Although this dosage of caffeine seems high, it is about one-half of the dosage, calculated on the basis of weight, administered daily (in beeswax) to the cats exhibiting gastric or duodenal ulcers. Computed upon the basis of milligrams per kilogram of average body weight of both cats and pouch dogs used, an equivalent dosage of caffeine in pouch dogs of average weight would be approximately 2,500 mg. In the light of this calculation four Pavlov and two Heidenhain pouch dogs were injected intramuscularly with 2,500 mg. of freshly prepared caffeine alkaloid in beeswax for four consecutive days (see Table V *B*).

These pouch dogs were injected at 9 A.M. and four one-hour samples of pouch secretions were collected. These samples were titrated for free and total acid as previously described. At 1 P.M. the animals were returned to their cages and given identical diets and water. At 5 P.M. the food pans were removed, although water was allowed up until the test period of the following day. This procedure was repeated on four consecutive days.

In each instance (see Fig. 3) a severe stimulation effect was noted with a marked increase in free acid and volume of the pouch secretions after an initial fall in values. In Dogs 20, 44, and 16, a decrease in the expected response after the third injection of the drug suggests some defect in the preparation injected that day. On the following day, the injections evoked once again the response previously observed. During this four-day test period no symptoms other than mild anorexia and lethargy were noted.

The injections of this same material without caffeine in other pouch dogs evoked no significant secretory response.

Three experiments with two Pavlov pouch dogs were carried out by injecting intramuscularly 2,500 mg. of caffeine alkaloid in beeswax according to the plan previously described. However, daily when the samples were collected, at the peak of the caffeine stimulatory response, atropine sulfate, gr. $\frac{1}{100}$, was injected intramuscularly at a different site. Although the response was somewhat less than anticipated for the following two or three hours, the stimulatory effect of caffeine could not be inhibited. These results are tabulated in Table V *B* but were not included in Fig. 3.

Roth and Ivy[9] were unable to demonstrate a gastric secretory response in dogs by the subcutaneous, intramuscular, and intravenous routes with 250 mg. of caffeine sodium benzoate. They observed a stimulatory response in cat and man. These investigators implied that a species difference might be present. Their results are not in accord with our own experimental data. It is true that in the smaller dosages used, no stimulatory response is produced. However, in our experiments, when dogs (on the basis of body weight) were given caffeine in the magnitude of that dosage necessary to produce ulcers in cats, a definite severe stimulatory response of gastric acidity and volume was recorded.

III. *Effect of Caffeine on Gastric Secretion in Man.*—Having established the fact that caffeine does stimulate gastric acidity and is capable of producing ulcers in smaller animals, an attempt was then made to study the effect of caffeine on human gastric acidity. Obviously, to be

of significance, the dosage of caffeine administered had to be in the range of that ingested in everyday activity. Coffee, a universal beverage, was chosen as the test substance. Coffee is known to contain ingredients other than caffeine. These substances are present, however, in minimal amounts. As all the pharmacologic actions of this beverage are essentially those of the alkaloid caffeine, in all probability the effect on gastric secretion can be attributed directly to the caffeine content. The

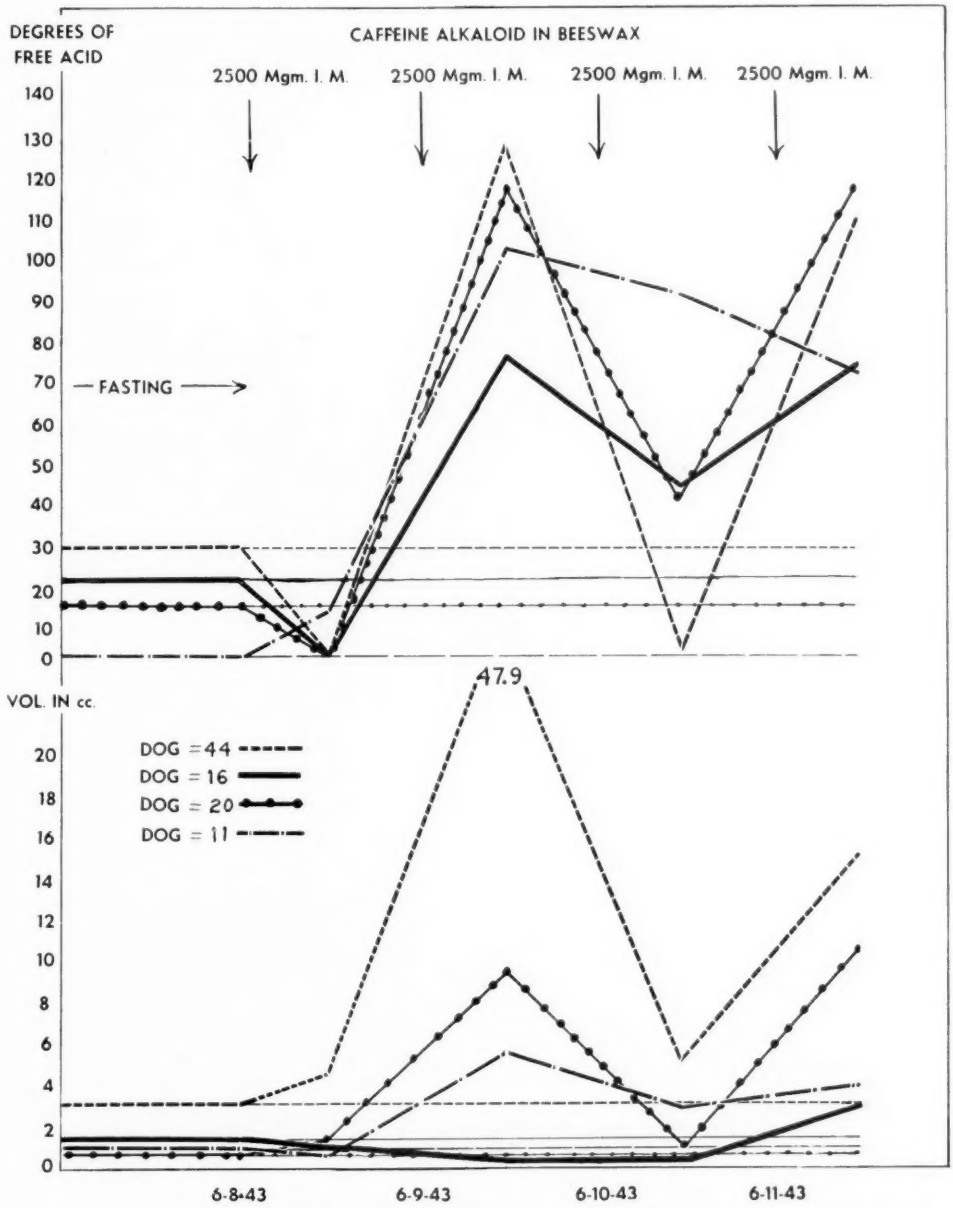


Fig. 3.—Pavlov pouch Dogs 16 and 11, and Heidenhain pouch Dogs 44 and 20. Daily 2500 mg. of caffeine in beeswax were injected intramuscularly for four days. Pouch juice was collected hourly for a four-hour period. This specimen was measured and analyzed for free acid. The points on the graph represent the average free acid and volume per hour of each dog for that particular day.

coffee was used directly from the University Hospital's kitchen at a time when it was being served throughout the hospital.

Patients were chosen at random without reference to age, drinking habits, or primary disease. A light dinner was given the evening before

the test day. On the following day breakfast was omitted. Water was allowed up until but not during the experiment. During this period water was given for a mouthwash as desired. The patient was admonished not to swallow it. No other medication was permitted during the test period.

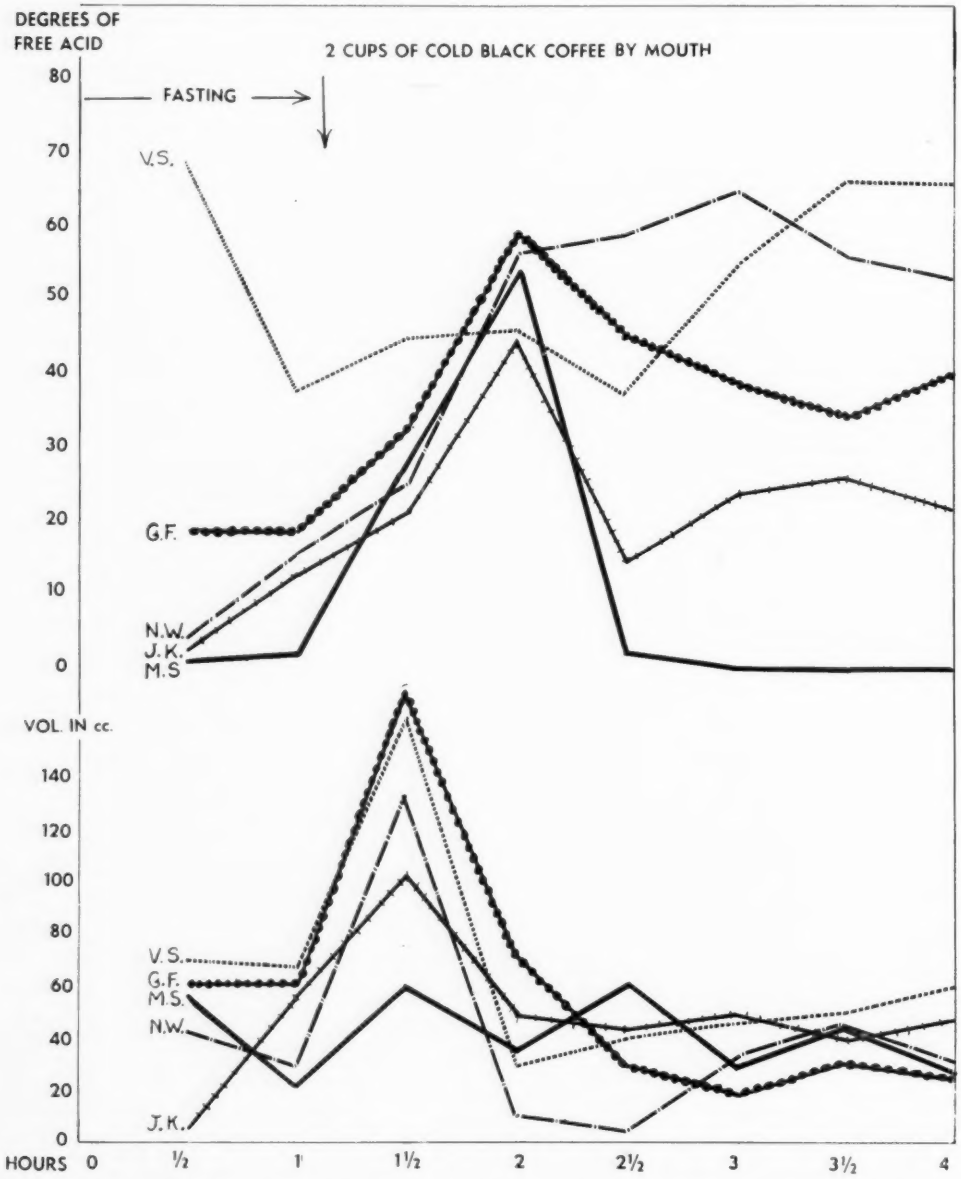


Fig. 4.—This graph represents the gastric secretory response of five individuals. Continuous nasal suction was applied. Two one-half hour fasting samples were obtained. Two cups of cold black coffee were taken by mouth. One-half hour was allowed to elapse, following which continuous nasal suction was restarted. This one-hour lapse of time is not charted in the graph. A stimulation of free acid and volume occurred in four of five tests. One patient (M.S.) had been hospitalized for a chronic duodenal ulcer.

At 8 A.M. a nasal tube was passed into the stomach and continuous suction was instituted. Two fasting samples of gastric juice were obtained at one-half hour intervals. These samples served as our controls. Suction was discontinued and two cups of coffee were given the patient. One-half hour later suction was reinstituted and continued for three

subsequent hours. During this three-hour period one-half hour samples of gastric juice were collected in individual tubes. These eight specimens (including the fasting specimens) were titrated against 0.1 N sodium hydroxide using Toepfer's solution and phenolphthalein as indicators for free and total acidity. All samples were measured to 0.1 cm.

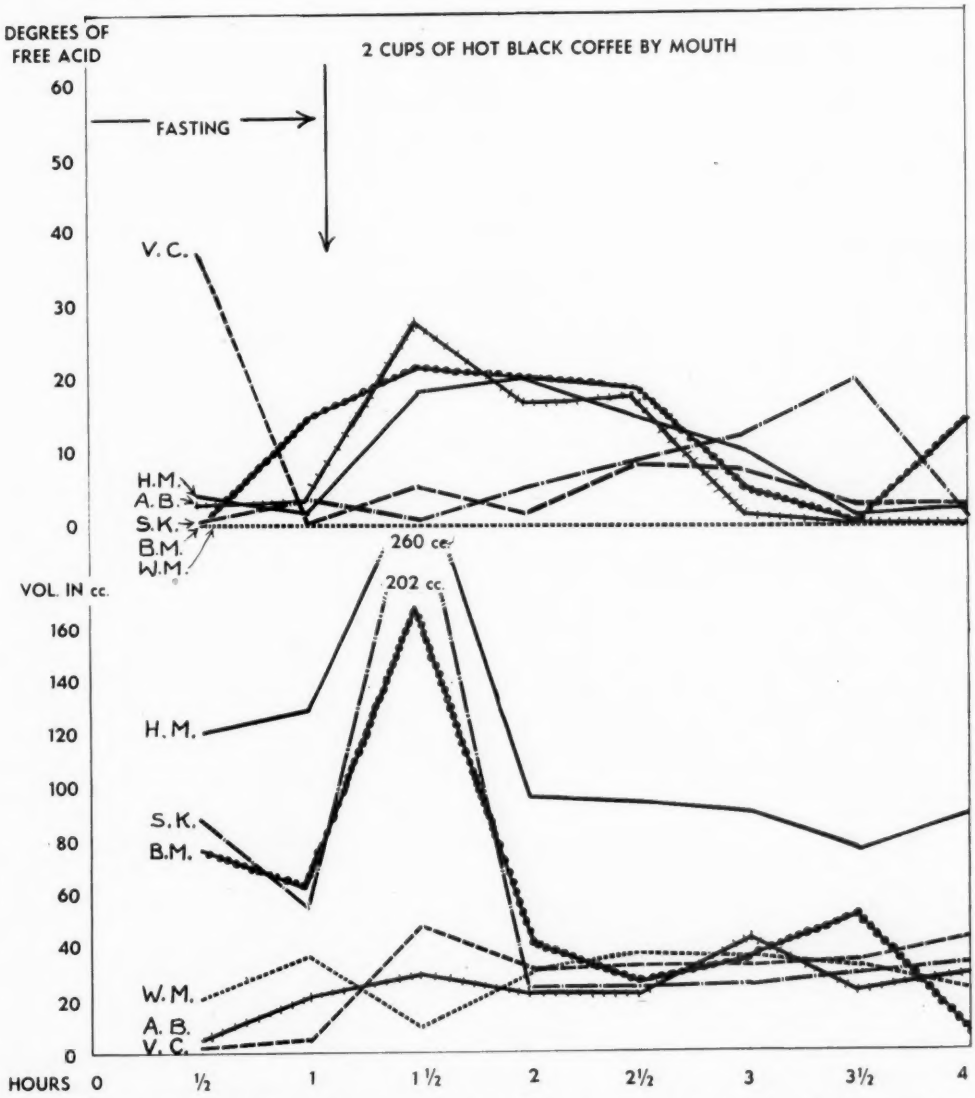


Fig. 5.—In this graph is recorded the gastric response of six individuals allowed two cups of hot black coffee by mouth. One patient (V.C.) had a proved gastric ulcer. Another patient (W.M.) secreted no free acid throughout the experiment. No opportunity arose to test this patient later with histamine. Achlorhydria may have been present. In general, the acid response with hot coffee was not as striking as the response with cold coffee.

In all experiments, black coffee without sugar or cream was used in order to avoid the possible side effects of the latter two substances. In certain experiments hot coffee was given, in others, cold coffee. By this means it was possible to evaluate the thermal effect, if any, on the gastric secretion. Further, in some instances the coffee was injected through the nasal tube. No information was given the patient regarding the nature of the liquid instilled; in other experiments the patient was allowed to drink the coffee by mouth. In this fashion, the factor of psychic stimulation (cephalic phase) of gastric secretion was controlled.

A total of nineteen such experiments were carried out. In fourteen tests (73.60 per cent) a definite stimulatory effect on gastric acidity and volume was noted.

For convenience these experiments have been grouped into the following categories:

1. Two cups of cold black coffee by mouth.
2. Two cups of hot black coffee by mouth.
3. Two cups of cold black coffee through the nasal tube.
4. Two cups of hot black coffee through the nasal tube (see Figs 4, 5, 6, and 7).

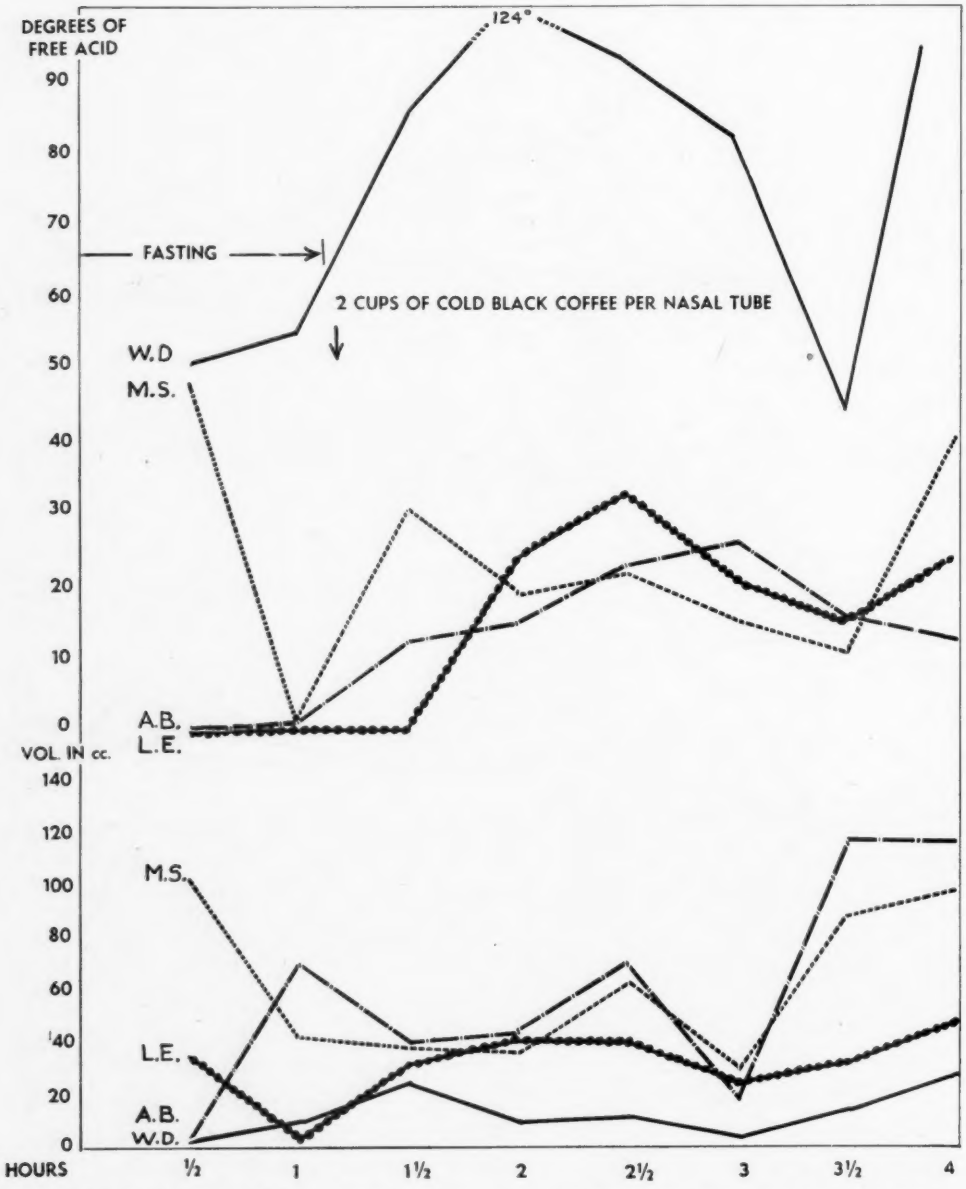


Fig. 6.—In these four patients two cups of cold black coffee were injected into the stomach through the nasal tube. The patients had no knowledge as to the type of material instilled. In three experiments a stimulatory response was evoked. Occasionally a secondary or late stimulation of free acid and volume was observed. This also was noted in other tests.

In each separate category a stimulatory effect was noted in the majority of instances. The severest stimulation effect was observed in those cases in which cold black coffee was given by mouth; these results were approximated by the group of patients receiving cold black coffee by nasal tube. The stimulation of acid with hot black coffee by nasal

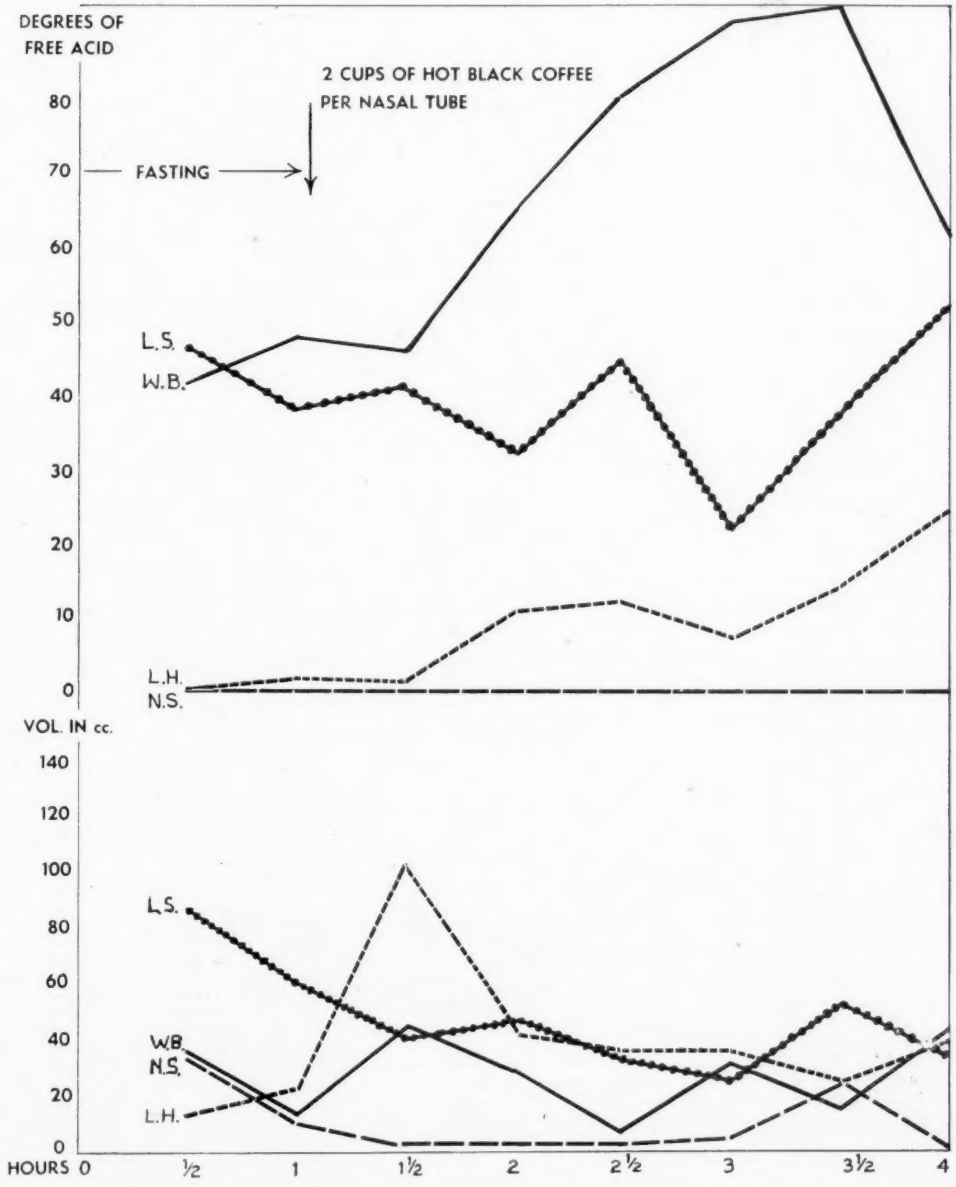


Fig. 7.—Two cups of hot black coffee were instilled by nasal tube into the stomach. Two patients, (L.S. and L.H.) three hours after the injection, began to show a secondary rise in free acid observed previously. One patient (N.S.) revealed no free acid throughout this test. We were unable to establish later his response to histamine. Perhaps this patient was achlorhydric.

tube was not as marked as in those patients allowed the hot coffee by mouth, although large volumes of gastric juice were secreted. In the main however, the stimulation of acid in these groups was not of the same magnitude as the stimulation noted in the groups in which cold coffee was used.

Then, seven patients were tested in the same manner as previously described. In addition to two cups of cold black coffee by mouth, these patients were injected intramuscularly with atropine sulfate, gr. $\frac{1}{75}$. No constant decrease of the stimulatory effect was observed, although there was a temporary decrease in certain instances.

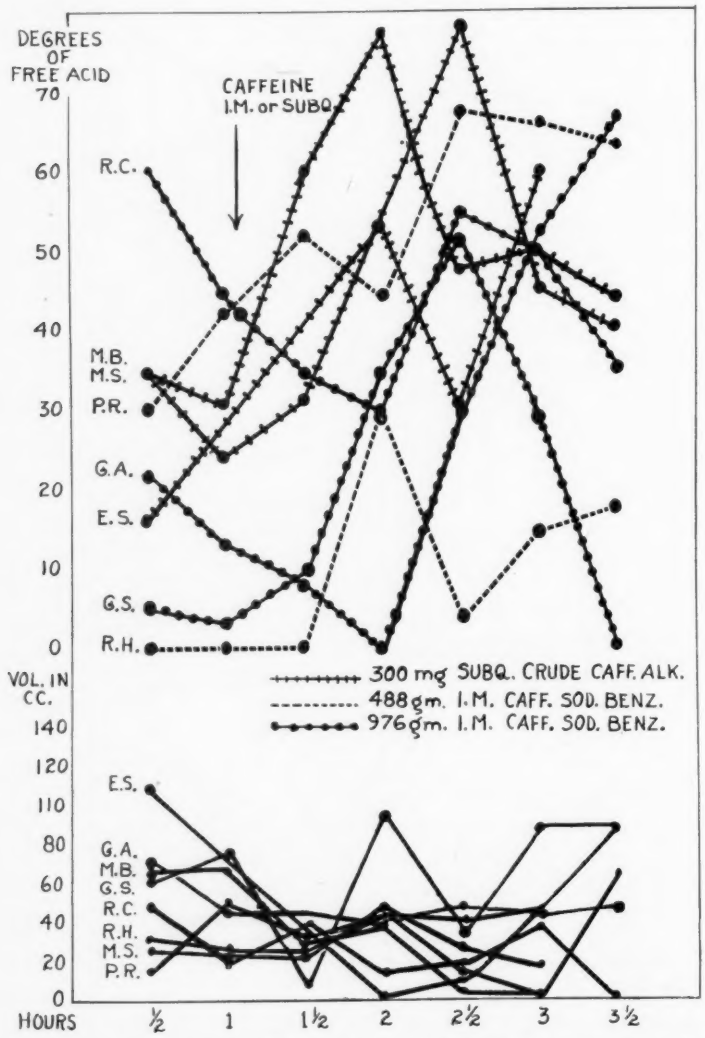


Fig. 8.—These tests were carried out by injecting subcutaneously or intramuscularly aqueous caffeine alkaloid and caffeine sodium benzoate. Both drugs contain 50 per cent caffeine. A moderately severe stimulation of gastric free acid was noted in seven of the eight experiments carried out. The only exception was a patient (R.C.) who had a proved duodenal ulcer. Caffeine sodium benzoate, 976 mg. (gr. 15), intramuscularly produced no stimulation of gastric secretions.

To strengthen further our hypothesis that the stimulatory effect on gastric secretions obtained in human beings with coffee was due to the caffeine present, the following experiments were carried out.

These tests reduplicated in all details the experiments with coffee with two exceptions, namely: (1) that continuous nasal suction was applied throughout (a lapse of one-half hour occurred after coffee was given), and (2) that after the two one-half hour fasting specimens were obtained, synthetic caffeine-containing drugs were injected subcutaneously, intramuscularly, or intravenously.

Fourteen such experiments were performed. Three experiments were unsatisfactory. In one patient's "gastric" samples the material obtained was heavily colored with bile. This suggested that the nasal tube was in the duodenum. Two individuals revealed no free acid throughout the test period with caffeine. Subsequently these patients were tested with histamine. Both were completely achlorhydric. Therefore, these results were discarded.

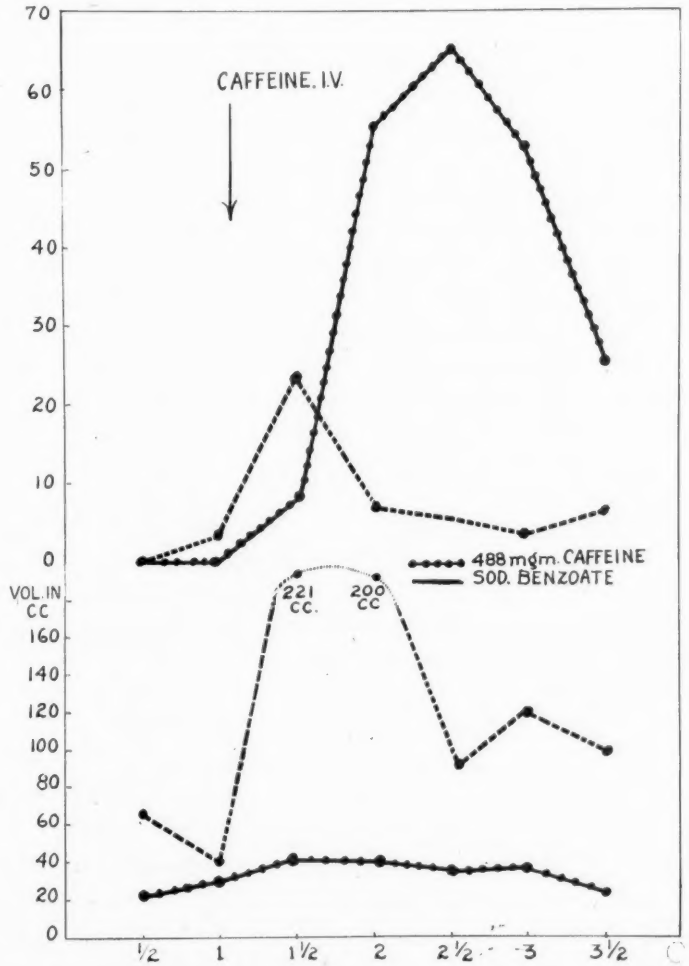


Fig. 9.—Both patients injected with 488 mg. (gr. 7 ss) of caffeine sodium benzoate intravenously revealed a stimulatory response. No untoward reactions were noted.

The eleven experiments considered to be satisfactory can be grouped as follows:

1. Three patients received 300 mg. of aqueous caffeine alkaloid subcutaneously.

2. Five patients received 488 (gr. 7 ss) to 976 mg. (gr. 15) of caffeine sodium benzoate intramuscularly.

3. Two patients received 488 mg. (gr. 7 ss) of caffeine sodium benzoate intravenously.

The crude caffeine alkaloid was dissolved in physiologic saline. One cubic centimeter contained 1 mg. of caffeine alkaloid. This solution was autoclaved by the method used in sterilizing all parenteral fluids in this hospital. This was administered as a hypodermoclysis into the thigh.

The caffeine sodium benzoate injected intramuscularly was prepared on the wards in the usual manner. This was administered into the deltoid muscle by means of an intramuscular needle. The intravenously administered caffeine sodium benzoate was dissolved in 10 c.c. of saline solution and injected into the antecubital vein.

Aqueous caffeine alkaloid and caffeine sodium benzoate contain 50 per cent of caffeine. Therefore, the actual amount of caffeine injected is one-half of the total dosage of the caffeine sodium benzoate or caffeine alkaloid administered.

In nine of the ten experiments performed (90 per cent), a definite stimulation of the gastric acidity was produced (see Figs. 8 and 9). There was occasionally a marked increase in the volume of gastric juice. This was the exception rather than the rule. In general, there was a slight to moderate increase in the volume of gastric juice secreted during the test period. In one instance, 996 mg. (gr. 15) of caffeine sodium benzoate injected intramuscularly evoked no stimulatory response. This occurred in a 30-year-old patient (R. C.) who had a proved duodenal ulcer. Although the usual response was not noted, this patient complained of epigastric pain. No significant side effects were noted in the other patients.

SUMMARY

When 200 mg. of crude caffeine alkaloid in beeswax were injected daily intramuscularly in a series of five guinea pigs, the toxic manifestations were so severe that death ensued too rapidly for any satisfactory data to be obtained. However, in a series of ten guinea pigs in which the dosage was reduced to 100 mg. of caffeine alkaloid in beeswax injected in a similar fashion, eight (80 per cent) guinea pigs developed some degree of upper gastroduodenal pathology. Four (40 per cent) exhibited "peptic" erosions or ulcers. Microscopically, these are typical ulcers similar to those found in man superimposed on a moderate to severe gastritis.

Cats receiving intramuscularly 300 mg. of caffeine alkaloid in beeswax daily exhibited upper gastrointestinal pathology in fourteen of twenty-six animals. Eleven of these cats (40 per cent) developed "peptic" erosions and/or definite ulcers.

In standardized pouch dogs, the subcutaneous injection of aqueous caffeine citrate and aqueous caffeine alkaloid in dosages up to 600 mg. produced no significant change in pouch acidity and volume. However, when the dosage of caffeine alkaloid was increased to 1,200 mg. a definite stimulation effect of pouch acidity and volume was observed.

This dosage in dogs was computed to be approximately one-half of the dosage used to produce ulcers in cats on the basis of milligram per kilograms of body weight. Consequently, four pouch dogs were injected with 2,500 mg. of caffeine alkaloid in beeswax intramuscularly for four consecutive days. A marked increase of pouch acidity and volume occurred.

These latter results suggest that the ulcers produced in cats by the injection of caffeine alkaloid in beeswax may well be explained on the basis of the stimulation of free acid.

Nineteen experiments were conducted on human beings. To evaluate the effect of coffee on gastric acidity and volume, these tests were devised to control the possible thermal and psychic effects of the coffee. The ingestion of cold coffee produced the most striking results. It is possible that the increased temperature of the hot beverage inhibited to some degree the gastric secretory response. Psychic stimulation appeared to be of no real significance. In eleven instances (73 per cent) a definite stimulatory effect on gastric acidity was observed. The variation in the volume of gastric juice was not striking.

In nine of ten experiments (90 per cent) in man, a striking stimulatory response of gastric acidity was observed when caffeine-containing drugs were administered parenterally (aqueous caffeine alkaloid, 300 mg. and caffeine sodium benzoate, 488 to 976 mg.).

Computed on the basis of milligram per kilogram of body weight, the dosage of aqueous caffeine alkaloid or caffeine sodium benzoate necessary to produce a stimulation of gastric acidity in man is approximately 4.3 mg. per kilogram of body weight. In guinea pigs plus-minus 200 mg. of crude caffeine alkaloid (in beeswax) per kilogram produced ulcers; in cats approximately 104.8 mg. of the same material per kilogram were necessary for ulcer formation. In pouch dogs (average weight 20 kilograms) a total dose of 1,200 mg. of aqueous caffeine alkaloid was needed to evoke a stimulation of gastric secretions in the majority of experiments. This is approximately 60 mg. of drug per kilogram. This dosage is twelve times the amount which regularly produces a moderately severe stimulation of gastric acidity in man. It is apparent that man's gastric secretory mechanism is exceedingly sensitive to caffeine stimulation. It is undoubtedly much more sensitive to the caffeine effect than is that of the dog. Further comparisons of dosage on the basis of body weight suggest also that man's gastric secretory apparatus is probably more sensitive to caffeine than both the guinea pig and the cat.

No important differential response in pouch secretion was observed in any experiments between the Heidenhain (vagus destroyed) and Pavlov (vagus intact) pouch dogs. The fact that a stimulatory effect was noted in the Heidenhain pouch dogs suggests that the vagus nerve is not necessary for the production of this effect. However, in Pavlov pouch dogs and in human beings, atropine sulfate seems to produce a minimal temporary depression in pouch and gastric secretions in certain instances. Therefore, the stimulatory effect of caffeine must occur mainly by direct action on the parietal cells of the stomach.

CONCLUSIONS

1. Typical "peptic" ulcers were produced in 40 per cent of guinea pigs and cats by the daily intramuscular injections of caffeine alkaloid in beeswax.

2. The subcutaneous injection of 1,200 mg. of aqueous caffeine alkaloid in pouch dogs caused a stimulation effect of pouch acidity and volume in 66⅔ per cent of the experiments. Similarly injected smaller doses of aqueous caffeine citrate and caffeine alkaloid produced no stimulation effect.

3. Pouch dogs injected with 2,500 mg. of caffeine alkaloid in beeswax for four consecutive days exhibited a marked and prolonged increase

of free acidity and volume of the pouch secretions. This dosage in dogs was equivalent to the dosage used to produce ulcers in cats. This suggests that the mechanism of ulcer production with caffeine is related to the increased production of free acid.

4. In 73 per cent of the human beings tested, two cups of black coffee caused a definite stimulatory effect on gastric acidity and volume. In all probability this can be attributed to the caffeine content of the coffee.

5. In 90 per cent of the human beings tested, aqueous caffeine alkaloid and caffeine sodium benzoate in 300 to 976 mg. doses evoked a moderately severe stimulation of gastric acidity and to a lesser degree volume, when administered subcutaneously, intramuscularly, or intravenously.

6. The gastric secretory mechanism in man is very sensitive to caffeine stimulation, much more so than that of the dog, and possibly the guinea pig and cat.

7. The stimulation effect observed with caffeine on the gastric and pouch secretions in man and dogs is mediated mainly through direct action on the parietal cells of the stomach. The effect of caffeine on gastric secretions apparently is not mediated through the vagus nerves.

8. These results suggest that the use of caffeine-containing beverages is contraindicated in the ulcer patient.

REFERENCES

1. Allard, E.: Ueber Theocinvergiftung, Deutsches Arch. f. klin. Med. **80**: 510, 1904.
2. Code, C. F., and Varco, R. L.: Chronic Histamine Action, Proc. Soc. Exper. Biol. & Med. **44**: 475, 1940.
3. Hanke, H.: Zur Pathogenese Der Experimentellen akuten und Erosiven Gastritis Infolge Parenteraler Zufuhr Bestimater Pharmaca (Morphin, Pilocarpin, Coffein), Klin. Wchnschr. **12**: 1524, 1933.
4. Hanke, H.: Experimentelle Erzeugung Chronischer Magengeschwüre Durch Coffein, Klin. Wchnschr. **13**: 978, 1934.
5. Hanke, H.: Zur Pathogenese der akuten erosiven Gastritis: Die Experimentelle Hämatogene Coffein Gastritis, Arch. f. klin. Chir. **178**: 607, 1934.
6. Judd, E. S.: Experimental Production of Peptic Ulcers With Caffeine, Interdepartmental Seminar, University of Minnesota, April, 1942; Abstracted in Bull. Am. Coll. Surgeons **28**: 46, 1943.
7. Molteni, M.: Lesioni Gastriche da Caffeina; Experimental Study, Arch. ital. di chir. **53**: 135, 1938.
8. Pincussohn, L.: Die Wirkung des Koffees und des Kakaos auf die Magensaftsekretion, München. med. Wchnschr. **53**: 1248, 1906.
9. Roth, J. A., and Ivy, A. C.: The Effect of Caffeine Upon Gastric Secretion in the Dog, Cat and Man, Am. J. Physiol. **141**: 454, 1944.
10. Roth, J. A., Ivy, A. C., and Atkinson, A. J.: Caffeine and "Peptic" Ulcer. Relation of Caffeine and Caffeine Containing Beverages to the Pathogenesis. Diagnosis and Management of "Peptic" Ulcer, J. A. M. A. **126**: 814, 1944.
11. Salant, W., and Rieger, J. B.: The Toxicity of Caffeine, J. Pharmacol. & Exper. Therap. **1**: 572, 1909.
12. Sollmann, T.: A Manual of Pharmacology, Ed. 5, Philadelphia and London, 1936, W. B. Saunders Company.

THE PEDICLED JEJUNAL TRANSPLANT ONTO THE GASTRIC WALL

Evaluation of Its Effect Upon Gastric Acidity and Failure of Such Transplants to Afford Protection Against Ulcer Provoked by Histamine in Beeswax

Fred Kolouch, Jr., M.D.,* Alfonso T. S. Dubus, M.D.,† and Owen H. Wangensteen, M.D., Minneapolis, Minn.

(From the Department of Surgery, University of Minnesota Hospitals)

ANDRUS and his associates have devised a surgical technique which, according to their observations, proved valuable in the treatment of experimentally produced ulcer in the dog as well as in the surgical management of spontaneously occurring acid-peptic ulcer of man. The operation consists of creating a defect in the gastric wall and implanting into it a short segment of jejunum, pedicled on its own blood supply. This transplant functions as a mucosal graft. The continuity of the jejunum is re-established by end-to-end anastomosis.

In experimental studies on dogs, Andrus and his associates[1-7] report that the jejunal graft caused a reduction in gastric acidity and an elevation of the pH of the gastric wall. The effects of the potent secretogogues, histamine and alcohol, were nullified they observed, and in some instances even reversed. The experimental production of peptic ulcer by the histamine and beeswax method was prevented, and on one occasion previously induced duodenal erosions healed in the face of continued postoperative stimulation. Quantitative studies showed an actual reduction of acid production of the parietal cells of the stomach and a slight increase in nonparietal secretion.

These investigators studied the mode of action of the implanted jejunal graft by instilling jejunal washings, obtained through a Thiry fistula, into the stomachs of dogs. The resulting diminution of acid secretion following histamine stimulation, they concluded, indicated the presence of an acid-controlling agent in the jejunum. Pedicled grafts which were taken from the jejunum proved to be more effective in influencing gastric acid secretion than duodenal grafts, which had only a slight effect; ileal and colonic segments were valueless. Gastrojejunostomy in dogs, they found, failed to influence gastric secretion, whereas the conversion of the parastomal mucosa into a pedicled graft caused a typical reduction in acidity.

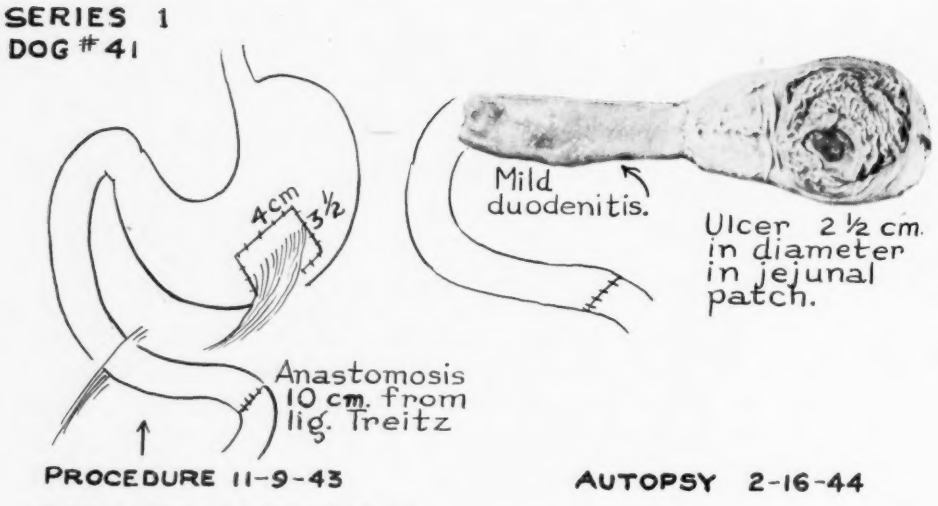
In the clinical application of the jejunal graft operation, they observed reduction of hyperacidity in three out of a total of four patients. The fourth patient showed clinical improvement with no concomitant change in acid secretion.

The researches presented here were supported by grants of the Citizens' Aid Society, the Augustus L. Searle and the Graduate School of the University of Minnesota.

*Fellow of the National Cancer Institute, Bethesda, Md.

†Fellow from one of the American Republics working at University of Minnesota Hospitals through the Inter-American Student and Professor Exchange at Washington, D. C.

Fig. 1



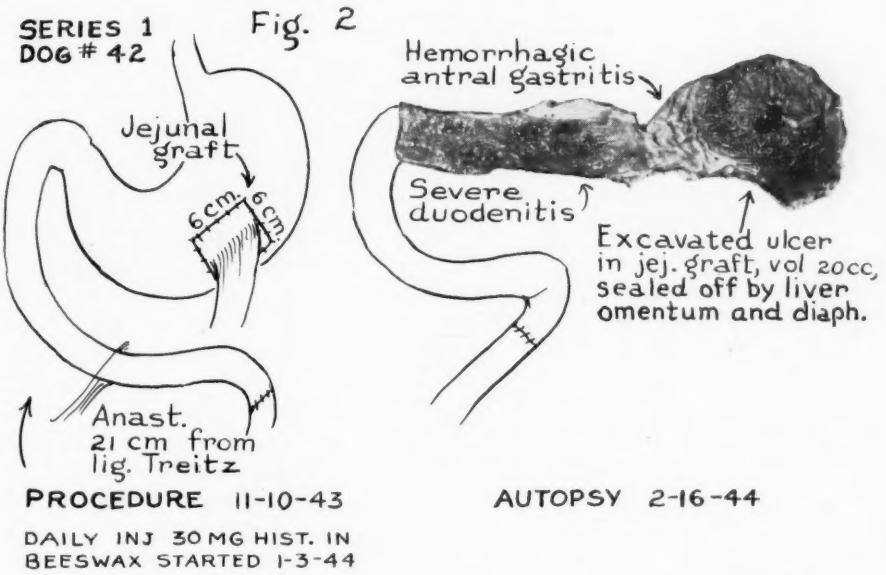
EXPERIMENT 1

Series 1, Dog 41. Mongrel male, weight 36 pounds (Fig. 1)

10/22/43	Distemper vaccine given
11/ 9/43	Jejunal graft operation
1/ 3/44	Daily injections 30 mg. of histamine in beeswax started
2/16/44	Weight 31 pounds, lost 5 pounds, general condition fair, sacrificed

Results of Gastric Analyses

DATE	SAMPLE (HR.)	VOLUME (C.C.)	FREE ACID (DEGREES)	TOTAL ACID (DEGREES)	pH
12/14/43	Fasting	9.5	4.49	16.13	4.51
	½	24.5	118.08	128.44	1.54
	1	5.4	8.17	16.34	3.32
	1½	5.3	0	6.46	6.41
	2	11.0	2.04	16.34	6.54
12/15/43	Fasting	44.0	0	12.25	6.9
	½	51.5	60.85	72.90	1.36
	1	16.0	62.49	77.80	1.44
	1½	7.0	21.03	49.01	1.64
	2	11.0	2.04	10.41	6.18
12/17/43	Fasting	33.0	1.6	11.6	7.19
	½	29.0	71.5	82.7	1.23
	1	17.0	51.1	91.3	1.44
	1½	4.7	0	11.0	7.28
	2	24.0	0	5.9	7.30
12/21/43	Fasting	0.8	0	24.25	8.55
	½	49.0	85.76	100.06	1.58
	1	24.0	43.09	67.18	1.50
	1½	15.0	1.84	24.10	4.05
	2	3.8	8.75	30.93	2.14



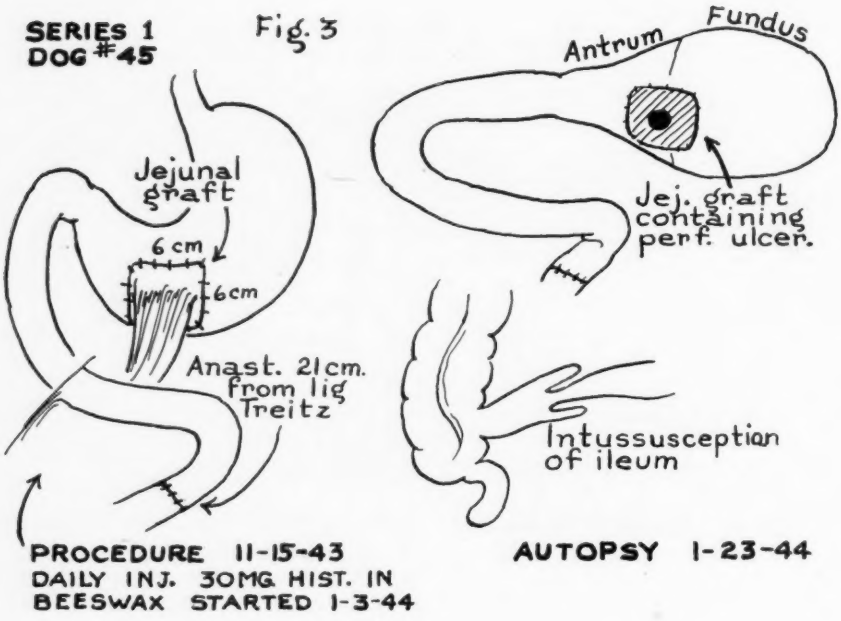
EXPERIMENT 2

Series 1, Dog 42. Mongrel male, weight 50 pounds (Fig. 2)

11/10/43	Jejunal graft operation
1/ 3/44	Daily injection of 30 mg. histamine in beeswax started
2/16/44	Weight 40 pounds, dog ill, lost 10 pounds, sacrificed, autopsy

Results of Gastric Analyses

DATE	SAMPLE (HR.)	VOLUME (C.C.)	FREE ACID (DEGREES)	TOTAL ACID (DEGREES)	pH
12/14/43	Fasting	15.0	14.09	36.55	1.76
	½	14.0	61.26	75.15	1.58
	1	51.0	89.03	102.10	1.55
	1½	5.8	2.04	6.13	5.30
	2	23.5	30.22	44.72	1.67
12/15/43	Fasting	5.5	1.84	7.96	6.56
	½	50.0	83.52	95.97	1.34
	1	40.5	73.51	79.03	1.50
	1½	9.0	0	4.7	6.96
	2	3.1	0	4.08	7.46
12/17/43	Fasting	1.2	0	9.2	8.34
	½	30.0	38.8	52.5	1.51
	1	42.0	79.6	91.9	1.39
	1½	17.0	1.42	6.1	6.29
	2	1.1	0	9.2	8.01
12/23/43	Fasting	7.0	0	12.46	8.06
	½	32.0	77.60	91.07	1.53
	1	25.0	73.10	83.72	1.46
	1½	4.1	1.27	5.11	7.10
	2	13.0	0.82	11.23	7.14
12/30/43	Fasting	7.0	1.84	7.76	5.73
	½	101.5	85.56	117.42	1.18
	1	75.0	103.11	115.99	1.27
	1½	9.5	0	19.20	6.99
	2	2.8	0	20.42	7.67



EXPERIMENT 3

Series 1, Dog 45. Mongrel male, weight 45 pounds (Fig. 3)

11/15/43 Jejunal graft operation
1/ 3/44 Daily injections of 30 mg. of histamine in beeswax started
1/23/44 Expired, autopsy

Results of Gastric Analyses

DATE	SAMPLE (HR.)	VOLUME (C.C.)	FREE ACID (DEGREES)	TOTAL ACID (DEGREES)	pH
12/14/43	Fasting	6.2	10.21	24.71	3.40
	½	15.0	98.02	109.86	1.49
	1	53.5	113.13	120.27	1.28
	1½	32.0	67.39	77.60	1.38
	2	25.5	48.60	59.01	1.61
12/15/43	Fasting	13.0	1.02	14.29	6.54
	½	63.0	93.93	102.51	1.46
	1	43.0	89.85	100.06	1.54
	1½	17.0	63.30	77.60	1.41
	2	8.0	0	8.17	6.56
12/21/43	Fasting	6.6	0	20.42	7.02
	½	25.5	36.76	59.01	1.70
	1	3.7	0	20.42	7.11
	1½	17.0	0	26.55	6.73
	2	5.1	0	27.57	7.85
12/23/43	Fasting	1.1	0	10.22	5.66
	½	34.0	59.42	71.47	1.46
	1	32.0	59.22	72.70	1.47
	1½	4.5	1.13	6.80	6.93
	2	17.0	1.02	10.21	7.64

THIS STUDY

The interesting findings reported by Andrus and his associates suggested that this observed novel effect of a small jejunal pedicled graft on gastric acid secretion should be studied further. Our studies have been limited to an investigation of the effect of the pedicled jejunal graft on gastric secretion in dogs.

Method.—Preparation of the dogs for surgery consisted of deworming them with Nema capsules and placing them in individual cages. Their diet was composed of table scraps with a daily supplement of prepared dog food, 200 Gm. of horse meat, six tablets of brewers' yeast, and 50 mg. of cevitamic acid.

EXPERIMENT 4

Series 1, Dog. 93. Mongrel female, weight 28 pounds (Fig. 4)

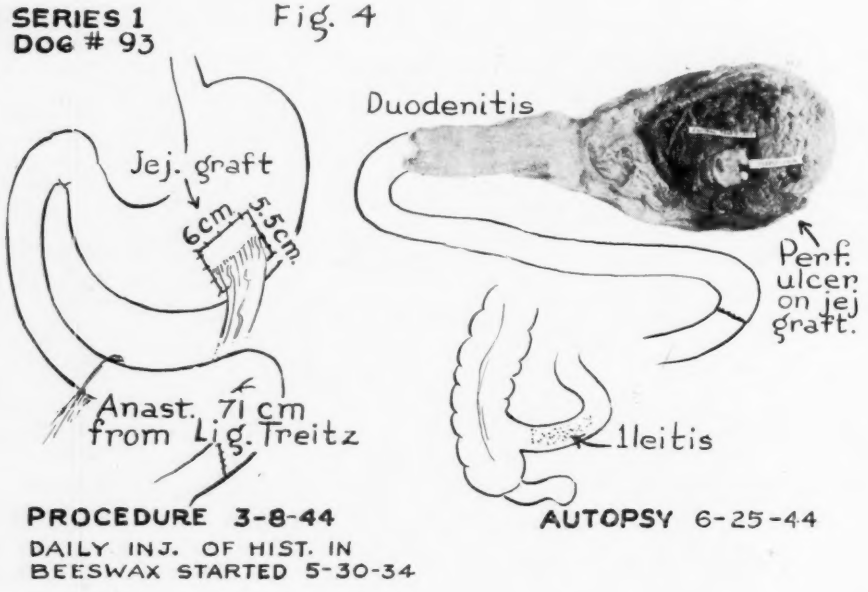
1/19/44	Dewormed
3/ 8/44	Jejunal graft operation
5/30/44	Daily injection of 30 mg. histamine in beeswax started
6/25/44	Expired, autopsy

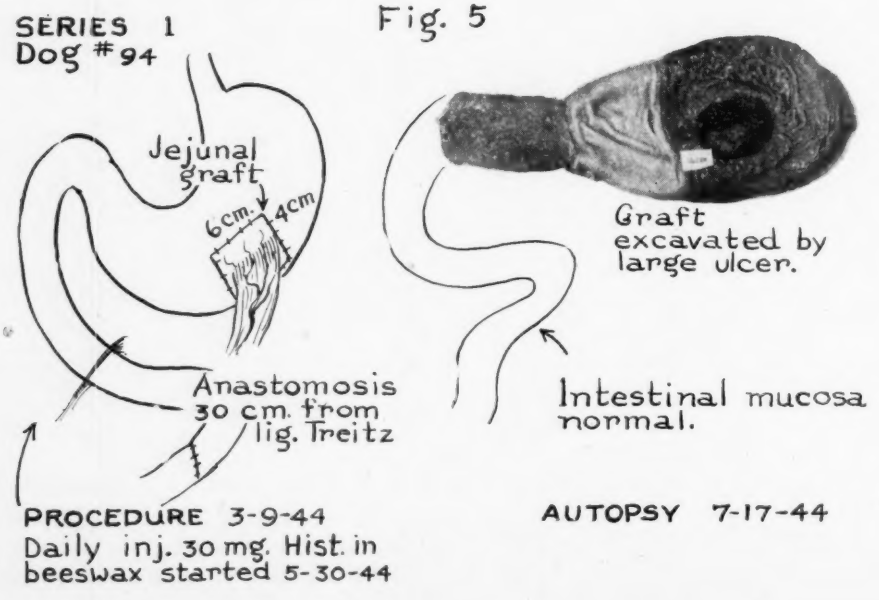
Results of Gastric Analyses

DATE	SAMPLE (HR.)	VOLUME (C.C.)	FREE ACID (DEGREES)	TOTAL ACID (DEGREES)	pH
1/21/44	Fasting	16.5	0	10.97	5.23
	½	72.0	105.48	117.37	1.17
	1	10.1	2.08	18.34	5.59
	1½	0.7	20.84	31.26	2.53
	2	1.7	2.78	9.03	5.83
1/24/44	Fasting	0.05	0	20.0	Too small
	½	83.0	79.4	87.53	1.26
	1	2.4	5.0	19.0	3.65
	1½	2.9	3.6	20.0	3.73
	2	2.3	0	9.0	7.14
4/ 3/44	Fasting	9.7	0	10.42	6.46
	½	30.0	87.53	95.03	1.63
	1	8.3	31.47	47.52	1.98
	1½	4.8	2.08	9.12	7.03
	2	3.8	0	12.16	8.23
4/10/44	Fasting	13.0	0	8.34	6.60
	½	12.5	53.31	66.27	1.54
	1	13.5	25.22	40.01	1.95
	1½	6.3	0	6.25	7.62
	2	3.8	0	5.76	7.48
4/17/44	Fasting	17.0	0	7.29	7.43
	½	25.5	55.23	64.40	1.57
	1	0.1	52.10	93.78	Too small
	1½	10.0	2.29	10.84	6.54
	2	6.2	0	7.29	7.31
4/24/44	Fasting	5.2	0	12.30	7.54
	½	15.0	65.23	83.99	1.42
	1	1.5	41.68	76.38	1.85
	1½	7.5	0	10.42	6.54
	2	11.5	0	17.09	6.59
5/18/44	Fasting	3.1	7.0	39.27	2.41
	½	32.5	68.62	83.01	1.60
	1	45.0	66.68	76.21	1.55
	1½	3.0	0	14.58	6.86
	2	8.5	0	12.44	6.53
5/23/44	Fasting	0.32	0	16.23	Too small
	½	25.0	56.18	66.10	1.46
	1	40.0	91.56	101.48	1.34
	1½	17.0	62.21	71.73	1.43
	2				

Under strict aseptic surgical technique, the jejunal transplant to the stomach wall was carried out in precisely the same manner as described by Andrus. The size of the graft and the position from which it was taken in the small intestine will be described in the individual protocols.

All gastric analyses were made with the animal in a fasting condition, and without the use of anesthesia. The fasting gastric contents were obtained by means of a stomach tube, after which 0.5 mg. of histamine base was administered subcutaneously, and an aspiration was done every thirty minutes during the succeeding two hours. The volume was measured and the free and total HCl and pH were determined.





THE EXPERIMENTS

Three series of experiments were completed on a total of thirteen dogs.

Series 1.—The first series of experiments was carried out on a group of ten dogs. Seven were subjected to the jejunal graft operation (Dogs 41, 42, 45, 93, 94, 95, and 96) and three control dogs (Dogs 58, 59, and 60) were not operated upon. Gastric analyses were made on Dogs 58, 59, and 60, postoperatively only on Dogs 41, 42, and 45, and both preoperatively and postoperatively on Dogs 93, 94, 95, and 96. Eight dogs were subjected to continuous gastric hypersecretion by daily intramuscular implantation of histamine in beeswax (Dogs 41, 42, 45, 58, 59, 60, 93, and 94). Dog 95 succumbed after a subtotal gastric pouch operation. A Heidenhain gastric pouch containing the pedicled jejunal graft was made in Dog 96.

EXPERIMENT 5

Series 1, Dog 94. Mongrel female, weight 20 pounds (Fig. 5)

3/ 9/44	Jejunal graft operation
5/23/44	Triple histamine test
5/30/44	Daily injections of 30 mg. histamine in beeswax started
7/17/44	Sacrificed, autopsy, tolerated histamine very well

Results of Gastric Analyses

DATE	SAMPLE (HR.)	VOLUME (C.C.)	FREE ACID (DEGREES)	TOTAL ACID (DEGREES)	pH
1/19/44	Fasting	2.7	0	11.46	7.5
	½	15.1	44.18	60.44	1.54
	1	4.0	8.34	26.05	2.26
	1½		No sample		
	2		No sample		
1/21/44	Fasting	0.6	0	17.37	Too small
	½	42.5	95.86	102.53	1.28
	1	0.9	10.42	23.15	Too small
	1½	3.5	0	17.37	4.37
	2	1.82	6.51	35.17	Too small
4/ 3/44	Fasting	5.7	0	7.64	7.53
	½	20.5	56.06	66.69	1.78
	1	30.0	49.60	60.02	1.97
	1½	3.3	3.75	14.59	5.73
	2		No sample		
4/10/44	Fasting	7.3	0	10.42	7.05
	½	5.0	74.82	80.86	1.53
	1	17.6	6.25	16.67	1.44
	1½	2.0	0	6.25	7.23
	2	7.9	0	8.96	7.19
4/17/44	Fasting	7.0	27.09	43.56	1.83
	½	30.0	91.70	100.87	1.46
	1	4.3	2.64	7.55	6.56
	1½	4.9	1.16	4.63	6.85
	2	3.5	0	5.21	7.41
5/18/44	Fasting	6.0	0	5.83	6.92
	½	17.5	50.44	69.6	1.62
	1	30.0	80.87	95.26	1.52
	1½	18.0	34.21	56.18	1.65
	2	1.9	0	7.12	7.01
5/23/44	Fasting	15.0	30.13	44.52	1.63
	½	72.0	52.88	67.07	1.50
	1	42.0	65.90	75.62	1.50
	1½	37.0	71.93	81.07	1.46

EXPERIMENT 6

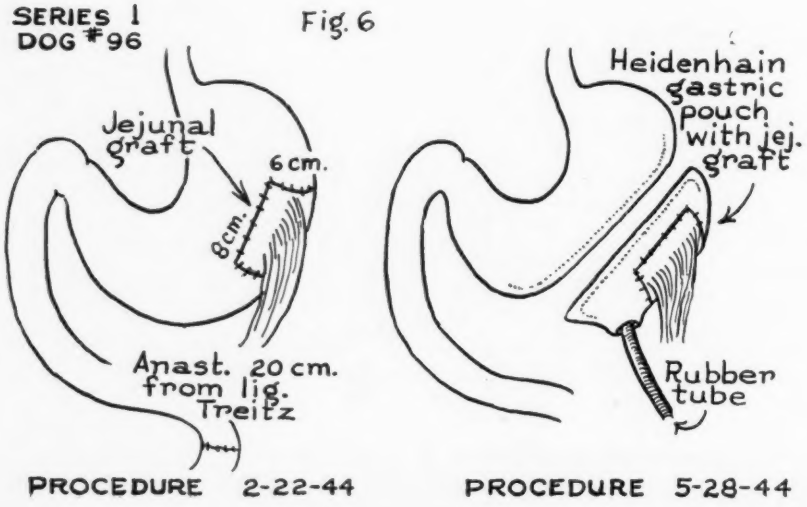
Series 1, Dog 95. Mongrel male, weight 25 pounds

2/24/44 Jejunal graft operation, graft 6 by 6 cm., taken 23 cm. from ligament of Treitz, placed on anterior surface of middle third of stomach

5/ 8/44 Subtotal gastric pouch; dog expired due to shock, autopsy

Results of Gastric Analyses

DATE	SAMPLE (HR.)	VOLUME (C.C.)	FREE ACID (DEGREES)	TOTAL ACID (DEGREES)	pH
1/19/44	Fasting	9.5	0	23.13	3.21
	½	48.2	112.33	120.68	1.00
	1	20.4	120.84	129.21	0.88
	1½	1.4	0	19.35	Too small
	2	0.2	0	41.68	Too small
1/21/44	Fasting	1.32	0	20.84	3.96
	½	97.3	106.28	116.92	1.26
	1	36.9	101.91	116.29	1.17
	1½	12.9	41.68	72.94	1.39
	2	5.0	3.13	56.27	1.53
1/24/44	Fasting	0.03	0	100.0	Too small
	½	65.0	100.03	114.2	1.28
	1	134.0	15.0	41.68	1.65
	1½	1.1	28.0	41.0	Too small
	2	0.65	5.0	23.3	Too small
4/ 3/44	Fasting	19.0	0	9.76	6.54
	½	55.0	76.90	89.40	1.55
	1	32.5	91.70	97.95	1.72
	1½	1.0	5.21	28.13	5.93
4/10/44	Fasting	5.1	0	15.0	7.30
	½	17.5	24.80	41.89	2.05
	1	24.6	20.84	39.60	2.14
	1½	8.7	0	12.5	6.65
4/17/44	Fasting	8.5	0	6.25	7.21
	½	60.5	87.32	96.07	1.33
	1	18.5	44.81	58.4	1.62
	1½	1.6	0	6.25	8.10
	2	0.8	0	13.03	Too small



EXPERIMENT 7

Series 1, Dog 96. Mongrel male, weight 36 pounds (Fig. 6)

2/22/44	Jejunal graft operation
5/28/44	Heidenhain pouch operation including jejunal graft
6/19/44	Gastric pouch analysis
6/20/44	Twenty-four-hour gastric pouch analysis
6/26/44	Twenty-four-hour gastric pouch analysis
7/ 5/44	Gastric pouch analysis
7/ 7/44	Gastric pouch analysis

Results of Gastric Analyses

DATE	SAMPLE (HR.)	VOLUME (C.C.)	FREE ACID (DEGREES)	TOTAL ACID (DEGREES)	pH
1/19/44	Fasting	10.1	10.21	81.07	2.11
	½	80.1	66.48	97.95	1.28
	1	20.1	47.51	81.28	1.35
	1½	4.1	17.56	47.33	2.85
	2	No sample			
1/21/44	Fasting	1.69	0	10.42	6.44
	½	43.0	66.69	82.94	1.32
	1	20.0	24.80	50.02	1.60
	1½	21.9	42.70	68.69	1.37
	2	20.9	62.50	78.15	1.30
4/ 3/44	Fasting	4.7	0	10.16	6.97
	½	17.5	74.61	83.57	1.98
	1	3.1	3.75	12.09	3.40
	1½	1.3	0	20.84	6.61
	2	0.9	0	72.94	Too small
4/10/44	Fasting	11.0	0	6.46	7.38
	½	29.5	67.73	82.94	1.40
	1	24.5	22.92	39.60	1.96
	1½	0.35	0	59.40	Too small
	2	3.5	0	71.45	8.08
4/17/44	Fasting	23.0	2.50	10.21	3.55
	½	35.5	83.36	92.53	1.76
	1	3.2	0.70	6.95	2.14
	1½	3.7	0	5.95	7.25
	2	5.1	0	5.21	7.88
5/18/44	Fasting	6.0	0	6.8	7.31
	½	35.5	55.02	64.15	1.70
	1	5.5	0	7.0	7.46
	1½	9.0	0	7.39	7.33
	2	3.7	0	9.36	7.56
5/23/44	Fasting	1.1	18.47	25.22	Too small
	½	15.0	33.05	40.24	1.73
	1	1.6	0	10.30	7.99
	1½	30.0	66.1	71.54	1.37

Results of Gastric Pouch Analyses

6/19/44	Sample 1	3.2	0	43.04	4.06
Stimulus:	Sample 2	0.6	0	32.28	Too small
0.5 mg.	1 N	31.0	109.75	123.09	1.09
histamine	2 N	4.6	96.30	103.83	1.25
subcuta-	3 N	1.5	38.74	55.95	2.20
neously					

EXPERIMENT 7—CONT'D

DATE	SAMPLE (HR.)	VOLUME (C.C.)	FREE ACID (DEGREES)	TOTAL ACID (DEGREES)	pH
6/20/44	Sample 1	1.4	68.40	93.00	1.73
Stimulus:	Sample 2	1.0	44.12	87.16	Too small
30 mg.	1 N	29.0	112.12	125.03	0.95
histamine	2 N	47.0	124.60	137.48	0.89
in bees-	3 N	49.0	122.02	128.26	0.99
wax	4 N	32.0	117.28	124.39	0.89
intramus-	5 N	4.83	115.99	122.23	0.96
cularly	6 N	16.0	120.51	129.55	1.07
	7 N	22.0	120.51	126.97	1.00
	8 N	18.6	107.17	112.23	1.04
	9 N	12.0	90.17	98.13	1.04
	10 N	15.0	113.63	119.87	0.94
	11 N	21.0	78.76	90.38	1.10
	12 N	9.0	25.82	38.52	1.57
	13 N	13.0	32.01	42.82	1.51
	14 N	18.0	77.90	90.38	1.23
	15 N*	23.0	44.98	122.66	1.40
	16 N*	17.0	69.29	118.79	1.24
	17 N*	26.5	79.62	114.49	1.20
	18 N	4.0	61.33	114.78	1.25
	19 N	5.0	0	51.11	2.95
	20 N	21.0	78.12	93.61	1.20
	21 N	14.0	73.17	81.56	1.17
	22 N	8.0	74.89	81.56	1.20
	Mixed samples				1.26
6/27/44	Sample 1	4.4	0	15.87	3.77
Stimulus:	Sample 2	2.4	0	32.08	7.20
30 mg.	1 N	33.0	121.59	141.82	0.94
histamine	2 N	45.0	140.31	161.18	0.99
in bees-	3 N	50.8	135.15	144.18	0.96
wax	4 N	46.5	131.27	140.1	0.89
intramus-	5 N	43.0	123.09	134.5	1.13
cularly	6 N	26.8	118.21	126.75	0.95
	7 N	20.3	109.32	108.14	1.03
	8 N	15.0	109.97	122.09	0.96
	9 N	10.0	109.54	123.09	0.99
	10 N	12.6	109.75	123.96	0.96
	11 N	5.2	98.99	118.58	1.09
	12 N	7.5	94.26	115.56	1.03
	13 N	7.8	68.86	125.89	1.17
	14 N*	1.8			3.66
	15 N*	2.0			4.00
	16 N*	2.8			4.74
	17 N*	2.7			4.66
	18 N*	1.6	Samples too bloody to do		4.30
	19 N*	1.2	free and total		4.12
	20 N*	5.3	acid determination		4.85
	21 N*	1.6			3.65
	22 N*	9.0			1.28
	23 N	No sample			
	24 N	No sample			
7/ 5/44	Sample 1	4.8	0	27.76	5.97
Stimulus:	Sample 2	2.6	0	29.05	5.00
0.5 mg.	1 N	28.0	94.90	112.12	1.17
histamine	2 N	3.8	20.33	59.70	1.80
subcu-	3 N	1.0	0	59.18	Too small
taneously					
7/ 7/44	Sample 1	3.6	0	53.75	2.95
Stimulus:	Sample 2	0.42	0	74.24	Too small
0.5 mg.	1 N	20.0	92.54	118.82	1.15
histamine	2 N	2.9	32.28	59.83	1.52
subcuta-	3 N	2.1	0	45.19	3.51
neously					

*Bloody samples.

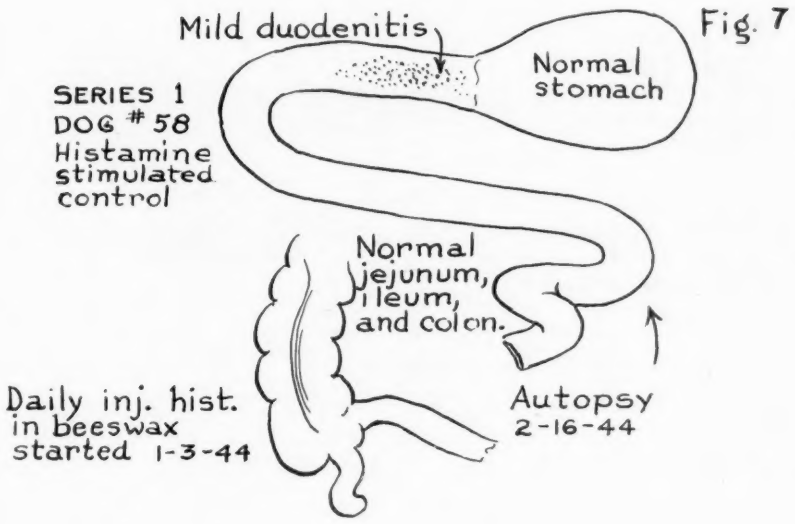


Fig. 7

EXPERIMENT 8

Series 1, Dog 58, Control dog.

Mongrel male, weight 35 pounds (Fig. 7)

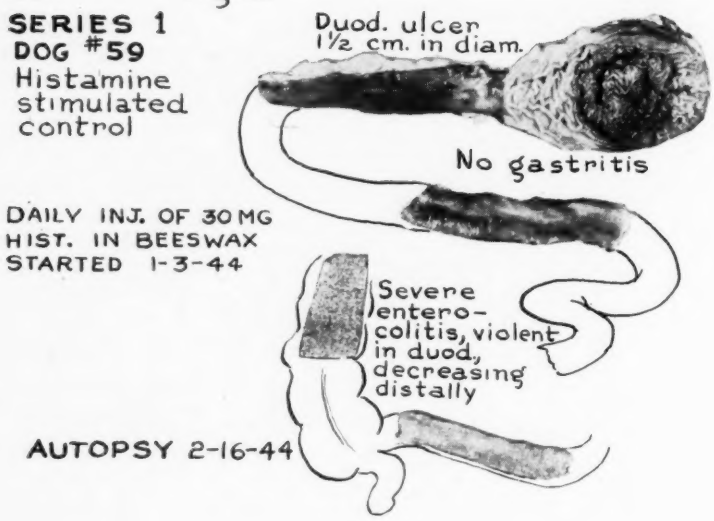
1/ 3/44 Daily injections of 30 mg. histamine in beeswax intramuscularly started

2/16/44 Sacrificed, autopsy performed

Results of Gastric Analyses

DATE	SAMPLE (HR.)	VOLUME (C.C.)	FREE ACID (DEGREES)	TOTAL ACID (DEGREES)	pH
12/14/43	Fasting	11.0	10.01	61.06	1.81
	½	35.5	140.90	158.26	1.40
	1	15.0	28.59	67.39	1.76
	1½	5.5	5.92	24.50	3.35
	2	0.5	0	20.42	Sample too small
12/15/43	Fasting	37.0	38.19	46.56	1.66
	½	66.0	102.10	118.44	1.24
	1	50.5	85.56	95.57	1.24
	1½	1.7	19.06	26.55	2.30
	2	2.8	2.04	7.35	1.44
12/17/43	Fasting	4.0	17.8	28.07	2.4
	½	45.0	110.3	124.6	1.54
	1	15.1	106.2	116.4	1.79
	1½	19.0	26.5	40.8	Not done
	2	6.0	30.6	46.96	1.7
12/21/43	Fasting	3.9	0	28.28	7.87
	½	66.0	113.94	124.97	1.71
	1	23.0	89.64	108.23	1.50
	1½	0.5	8.17	30.63	Too small
	2	1.2	2.04	10.21	Too small

Fig. 8


SERIES 1
DOG #59
Histamine stimulated control
Duod. ulcer 1½ cm. in diam.
No gastritis
DAILY INJ. OF 30 MG HIST. IN BEESWAX STARTED 1-3-44
Severe entero-colitis, violent in duod., decreasing distally
AUTOPSY 2-16-44

EXPERIMENT 9

Series 1, Dog 59, Control Dog.

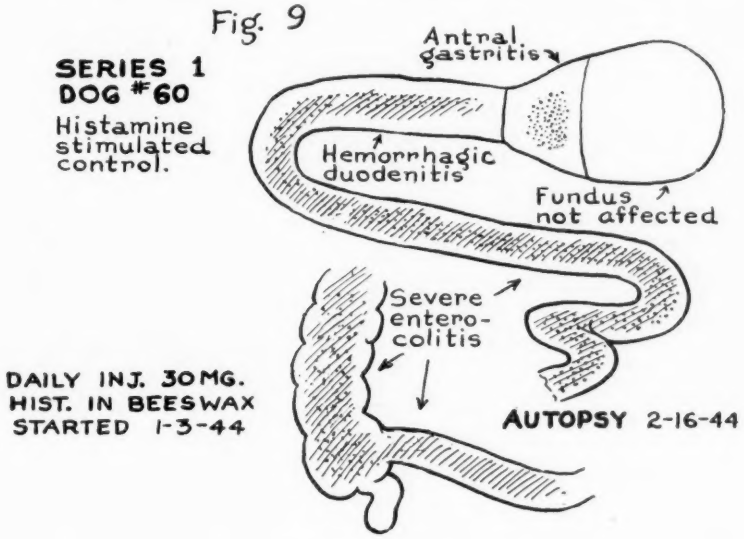
Mongrel male, weight 46 pounds (Fig. 8)

1/ 3/44 Daily injections 30 mg. histamine in beeswax started
2/16/44 Sacrificed, autopsy

Results of Gastric Analyses

DATE	SAMPLE (HR.)	VOLUME (C.C.)	FREE ACID (DEGREES)	TOTAL ACID (DEGREES)	pH
12/14/43	Fasting	5.5	42.27	63.10	1.60
	½	47.0	140.90	156.21	1.38
	1	52.0	134.77	146.00	1.39
	1½	5.3	1.84	5.92	5.96
	2	No specimen			
12/15/43	Fasting	0.8	0	12.25	7.10
	½	44.0	79.43	101.69	1.40
	1	8.0	7.96	40.64	1.61
	1½	16.0	9.60	17.97	5.13
	2	0.8	0	4.08	7.00
12/17/43	Fasting	4.5	0	20.4	7.11
	½	54.5	57.2	85.8	1.74
	1	44.5	81.7	100.06	1.54
	1½	3.0	6.9	18.7	3.05
	2	3.0	0	10.21	5.99
12/21/43	Fasting	16.0	0	40.43	7.17
	½	72.0	98.02	114.56	1.38
	1	25.5	83.93	97.81	1.65
	1½	13.0	26.55	41.04	1.85
	2	2.5	0	20.42	7.01

Fig. 9



EXPERIMENT 10

Series 1, Dog 60, Normal Control.

Mongrel male, weight 40 pounds (Fig. 9)

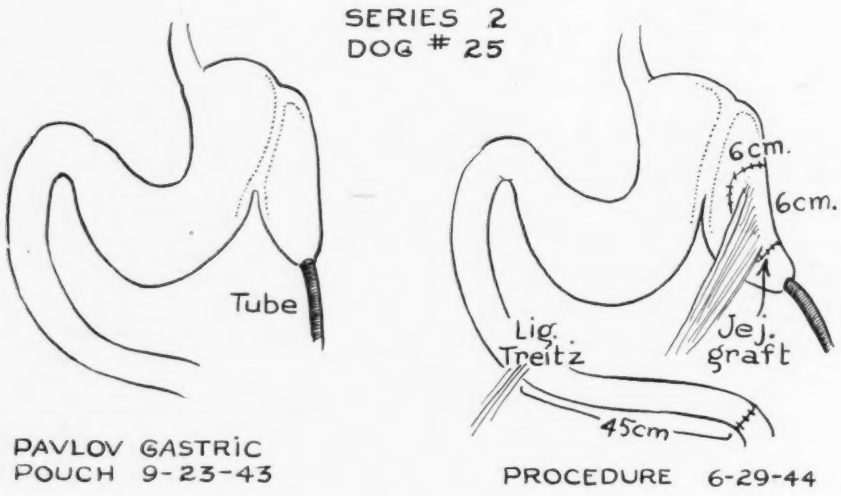
1/ 3/44 Daily injections of 30 mg. histamine in beeswax started
2/16/44 Sacrificed, autopsy

Results of Gastric Analyses

DATE	SAMPLE (HR.)	VOLUME (C.C.)	FREE ACID (DEGREES)	TOTAL ACID (DEGREES)	pH
12/14/43	Fasting	1.8	6.0	18.02	3.68
	½	110.0	138.86	144.98	1.31
	1	49.0	85.97	93.93	1.43
	1½	2.3	25.01	29.61	1.74
	2	14.0	3.06	12.86	6.46
12/15/43	Fasting	2.5	0	10.21	7.51
	½	96.0	130.48	138.65	1.25
	1	18.0	30.64	51.05	1.69
	1½	3.8	1.45	2.92	4.31
	2	2.4	0	5.11	6.94
12/17/43	Fasting	6.5	2.04	12.48	4.41
	½	55.0	115.78	127.22	1.41
	1	44.0	99.85	111.90	1.41
	1½	12.0	9.80	15.31	2.8
	2	5.3	1.84	8.58	7.56
12/21/43	Fasting	4.5	0	20.42	7.64
	½	36.0	139.06	152.95	1.26
	1	142.0	132.53	159.48	1.46
	1½	4.8	17.02	37.86	1.97
	2	2.0	20.42	36.25	3.06

Series 2.—The second series consisted of two dogs, one of which had a Pavlov type of gastric pouch (Dog 25) and the other a Heidenhain pouch (Dog 156). The response of these two pouches to gastric secretogogues was studied and recorded. Following these control observations, a pedicled jejunal graft was applied to the pouch of each animal. After a suitable healing period, the animals were exposed again to the same secretogogues and the response was observed. Analyses of the contents of the gastric pouches were made after the dogs were subjected to a twenty-four-hour fast. Two one-hour samples were obtained from each dog, the secretogogues were then administered, and the total output of gastric juice was collected at hourly intervals for from three to twenty-four hours.

Fig. 10



EXPERIMENT 1

Series 2, Dog 25. Mongrel male, weight 49 pounds (Fig. 10)

8/24/43 Distemper vaccination
9/23/43 Pavlov gastric pouch operation
6/29/44 Jejunal graft applied to Pavlov pouch

Results of Gastric Pouch Analyses

DATE	SAMPLE	VOLUME (C.C.)	FREE ACID (DEGREES)	TOTAL ACID (DEGREES)	pH
1/3/44	1	0.25	12.67	85.76	Too small
Stimulus: 0.5 mg.	2	0.30	34.00	51.05	Too small
histamine sub-	1 N	26.00	134.36	151.11	0.99
cutaneously	2 N	3.70	142.33	153.46	0.94
	3 N	1.60	84.41	110.27	1.20
1/5/44	1	0.15	6.81	61.26	Too small
Stimulus: 0.5 mg.	2	0.23	0	44.39	Too small
histamine sub-	1 N	5.0	134.16	147.02	1.07
cutaneously	2 N	2.0	130.68	141.92	1.08
	3 N	0.8	108.53	134.06	Too small
1/7/44	1	0.22	23.18	46.46	Too small
Stimulus: 0.5 mg.	2	1.5	0	40.80	3.43
histamine sub-	1 N	18.0	130.69	146.00	0.82
cutaneously	2 N	0.5	102.10	132.73	Too small
	3 N	0.12	84.74	170.51	Too small
5/29/44	1	2.4	0	122.47	3.63
Stimulus: 200 Gm.	2	1.1	0		Too small
horse meat fed	1 N	3.3	0	127.33	3.66
	2 N	6.0	55.6	129.66	1.50
	3 N	6.2	91.17	145.8	1.47
5/31/44	1	0.7	51.32	83.8	Too small
Stimulus: 200 Gm.	2	0.9	62.6	96.03	Too small
horse meat fed	1 N	6.0	107.11	122.08	1.61
	2 N	8.1	114.50	135.80	1.45
	3 N	7.4	119.94	139.97	1.37
6/2/44	1	No sample			
Stimulus: 200 Gm.	2	No sample			
horse meat fed	1 N	3.4	69.30	116.64	1.30
	2 N	3.2	85.51	131.22	1.17
	3 N	3.6	90.49	127.14	1.36
7/24/44	1	1.8	23.31	83.09	3.69
Stimulus: 0.5 mg.	2	1.6	28.24	79.96	2.76
histamine sub-	1 N	20.1	88.66	124.82	1.14
cutaneously	2 N	2.6	50.49	72.82	1.23
	3 N	0.98	7.98	17.56	1.0 (Hydrion)

EXPERIMENT 1.—CONT'D

DATE	SAMPLE	VOLUME (C.C.)	FREE ACID (DEGREES)	TOTAL ACID (DEGREES)	pH
7/28/44	1	2.4	0	112.76	3.59
Stimulus: 0.5 mg.	2	0.56	37.5	86.46	2.5 (Hydrion)
histamine sub-	1 N	24.0	126.75	152.79	1.27
cutaneously	2 N	1.4	84.54	123.74	1.6
	3 N	0.24	53.80	89.66	3.0 (Hydrion)
8/4/44	1	2.0	0	48.42	4.02
Stimulus: 200 Gm.	2	1.5	0	35.86	4.38
horse meat fed	1 N	5	0	58.1	3.05
	2 N	4.5	38.25	81.29	1.76
	3 N	6.5	38.74	90.38	1.66
8/9/44	1	1.8	0	37.66	3.54
Stimulus: 200 Gm.	2	1.0	0	53.80	5.5 (Hydrion)
horse meat fed	1 N	5.6	29.05	81.77	2.10
	2 N	11.0	94.69	118.36	1.87
	3 N	12.5	100.07	121.59	1.64

EXPERIMENT 2

Series 2, Dog 156. Mongrel female, weight 55 pounds (Fig. 11)

4/ 6/44 Heidenhain pouch operation
6/29/44 Jejunal graft applied to Heidenhain pouch

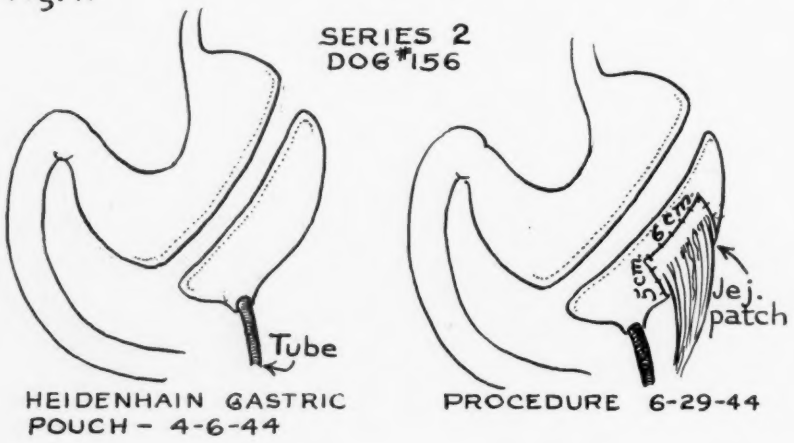
Results of Gastric Pouch Analyses

DATE	SAMPLE	VOLUME (C.C.)	FREE ACID (DEGREES)	TOTAL ACID (DEGREES)	pH
5/8/44	1	0.6	0	32.37	6.0 (Hydrion)
Stimulus: 0.5 mg.	2	1.2	0	21.38	5.87
histamine sub-	1 N	29.4	124.22	137.83	1.62
cutaneously	2 N	14.3	111.78	127.33	1.34
	3 N	0.8	75.8	126.74	1.5 (Hydrion)
5/10/44	1	1.4	0	23.91	7.62
Stimulus: 0.5 mg.	2	1.3	0	34.02	7.23
histamine sub-	1 N	25.5	99.14	126.36	1.36
cutaneously	2 N	24.0	116.33	149.30	1.55
	3 N	1.9	16.23	27.02	2.09
5/12/44	1	0.1	19.44	97.2	Too small
0.5 mg. histamine	2	0.5	17.50	77.76	Too small
subcutaneously	1 N	27.0	118.58	130.44	1.11
	2 N	12.5	137.83	147.74	1.47
	3 N	0.4	21.38	106.92	Too small
5/15/44	1	3.0	0	15.16	6.83
Stimulus: 200 Gm.	2	1.4	0	28.19	7.47
horse meat fed	1 N	1.4	0	19.44	7.46
	2 N	2.0	92.91	97.20	1.36
	3 N	4.6	88.35	106.53	1.20
5/19/44	1	9.3	34.60	54.43	1.83
200 Gm. horse	2	0.38	55.51	86.09	Too small
meat fed	1 N	2.9	12.31	34.99	3.12
	2 N	9.0	58.32	74.26	1.61
	3 N	6.7	93.31	101.48	1.64
5/31/44	1	0.5	66.10	83.59	Too small
200 Gm. horse	2	3.4	3.21	29.74	2.55
meat fed	3	1.8	0	14.19	4.35
	1 N	1.1	0	10.69	Too small
	2 N	5.2	25.66	41.02	1.76
	3 N	0.4	112.75	129.28	Too small
	4 N	6.0	101.28	107.89	1.53
	5 N	0.45	119.56	139.00	Too small
	6 N	1.8	97.20	116.64	1.63
	7 N	5.1	123.44	134.33	1.48
	8 N	3.5	123.44	130.26	1.50
	9 N	3.3	119.56	130.25	1.50
	10 N	0.25	68.04	106.92	Too small

EXPERIMENT 2—CONT'D

DATE	SAMPLE	VOLUME (C.C.)	FREE ACID (DEGREES)	TOTAL ACID (DEGREES)	pH
7/24/44	1	8.0	0	104.58	3.95
Stimulus: 0.5 mg.	2	4.0	0	127.72	4.0
histamine sub-	1 N	59.4	111.04	143.75	1.12
cutaneously	2 N	5.4	68.86	133.74	1.5
	3 N	1.4	22.28	103.76	2.52
7/28/44	1	1.8	0	34.67	4.84
Stimulus: 0.5 mg.	2	5.6	0	31.85	5.42
histamine sub-	1 N	49.0	113.63	141.82	1.54
cutaneously	2 N	13.0	89.31	138.16	1.55
	3 N	2.1	51.43	111.9	1.5
	4 N	1.01	0	42.61	5.5 (Hydrion)
8/4/44	1	6.0	0	45.19	5.98
Stimulus: 200 Gm.	2	4.5	0	26.29	6.58
horse meat fed	1 N	17.5	0	77.42	3.23
	2 N	12.5	32.28	96.84	1.89
	3 N	15.0	25.83	105.45	1.78
8/9/44	1	4.0	0	21.52	7.61
Stimulus: 200 Gm.	2	4.2	0	23.21	7.44
horse meat fed	1 N	14.5	0	79.62	3.18
	2 N	15.9	86.0	119.44	1.90
	3 N	19.0	62.41	109.75	1.89
10/6/44	1	11.0	0	53.8	3.76
Stimulus: 0.5 mg.	1 N	61.0	29.0	93.0	2.4
histamine sub-	2 N	111.0	25.5	89.0	2.3
cutaneously	3 N	12.0	0	19.0	4.8
10/10/44	1	0.31	0		3.28
Stimulus: 100 c.c.	1 N	16.3	73.0	105.7	1.55
alcohol by	2 N	3.05	49.7	87.0	1.19
stomach tube	3 N	0.75	0	9.5	1.22
10/13/44	1	5.8	0	31.2	5.2
Stimulus: 200 Gm.	1 N	10.25	0	43.0	4.32
horse meat fed	2 N	20.2	36.0	95.0	1.31
	3 N	22.0	52.0	93.0	1.17

Fig. 11



Series 3, Experiment 1.—The final experiment consisted of testing the irritating effect on duodenal mucosa of gastric juice obtained by histamine stimulation both from an ordinary type of Heidenhain gastric pouch and from another similar pouch which had been modified by the application of a jejunal graft. Gastric juice was collected from both of these dogs and saved for the experiment to be described. On 6/21/44, a male mongrel (Dog 184) was anesthetized with sodium pentobarbital,

and a three and one-half inch section of duodenum was isolated and exteriorized with its blood supply intact. The segment was opened along the antimesenteric border, and the mucosa was exposed by suturing the cut edges to the underlying abdominal skin. Immediately after the operation, the two collections of gastric juice were dripped, one from the Heidenhain pouch, the other from the Heidenhain pouch to which the jeunal graft had been applied, through similar nozzles, onto separate areas of the exposed duodenal mucosa (see Fig. 12).

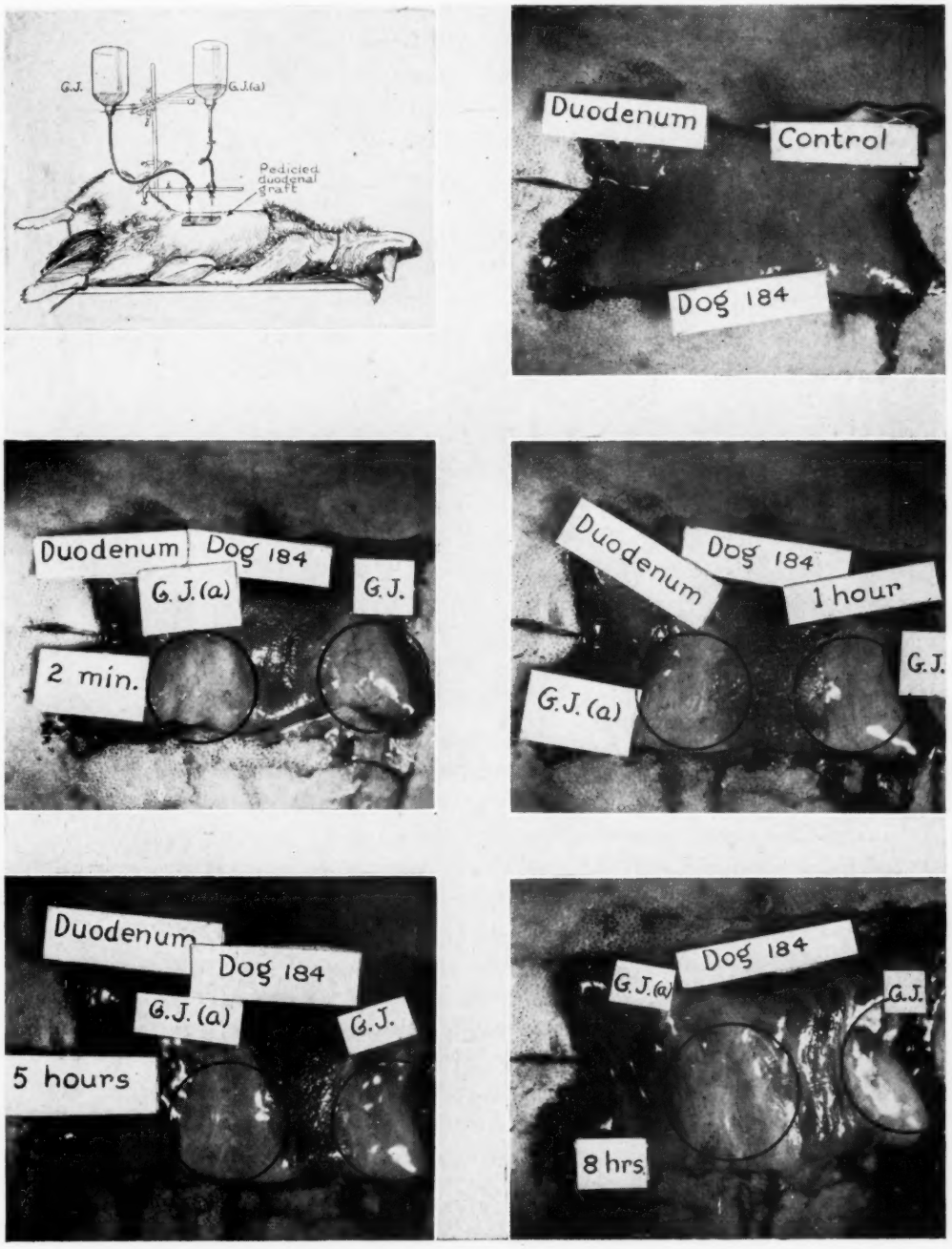


Fig. 12.—The photographs show the progressive effect of two samples of gastric juice on duodenal mucosa. *G.J.* indicates the area exposed to secretion obtained from an ordinary Heidenhain type of gastric pouch (Dog 156 before application of jejunal graft). *G.J.* (*a*) indicates the area exposed to gastric juice obtained from a Heidenhain pouch into which a jejunal graft had been implanted.

The effects of the two samples of gastric juice on duodenal mucosa varied little. In both of the dripped areas, edema and blanching occurred within two minutes. During the first ten to fifteen minutes, the reaction to normal gastric juice seemed greater, but within one hour, necrosis, edema, and hematin staining were of equal intensity in both areas. After five hours, two thick, gray, hematin-stained, mucosal sloughs were present. Gentle removal of the necrotic tissue by scraping with the edge of a piece of cardboard revealed equal pin-point hemorrhages beneath both the sloughs. At the end of eight hours' exposure to the gastric juice obtained both from an ordinary Heidenhain gastric pouch and from a Heidenhain gastric pouch into which a pedicled jejunal graft had been implanted, the duodenal mucosa exhibited damage of equal extent in both areas.

COMMENT

Investigation of the effect of the pedicled jejunal graft on secretory activity indicates that an irregular, inconstant, therapeutically ineffective depression of gastric acid secretion occurs.

Adequate gastric analyses over a period of two hours after the administration of 0.5 mg. of histamine base show a somewhat subdued, but in the main quite ordinary, response varying irregularly from dog to dog. A reversal of the histamine effect noted by Andrus and his associates was not observed on any occasion. In the continuous gastric hypersecretion experiments employing daily intramuscular injections of 30 mg. of histamine base in beeswax, the jejunal graft proved to be a locus of reduced resistance, and ulceration of the graft mucosa occurred in every dog with such a jejunal graft. In these same hypersecretion experiments, complete protection of the duodenal mucosa as observed by Andrus and his associates was not achieved in all cases. Duodenitis was observed in three out of five dogs with jejunal grafts applied to the stomach, given histamine in beeswax intramuscularly. In other words, it would appear that the jejunal graft itself when applied to the stomach is more sensitive to the acid peptic digestive juice than is the remainder of the stomach or the duodenum. Autopsies showed the pedicled blood supply of the graft to be satisfactory and intact in all animals. In experiments with the Heidenhain and Pavlov gastric pouches the implanted jejunal graft was found to be ineffective in regularly inhibiting gastric secretion from the isolated pouches. It may be fair to say that a small but inconstant depression of the acidity of the gastric secretion appears to attend attachment of the jejunal patch of the gastric pouch. Finally, gastric juice obtained from a Heidenhain pouch, modified by the application of a jejunal graft, proved to be as irritating as normal gastric juice when dripped onto exteriorized duodenal mucosa.

CONCLUSION

In conclusion, these experiments suggest that the jejunal graft is inefficient in controlling gastric and peptic secretion, and that it does not curb the digestive properties of gastric juice. In consequence, the pedicled jejunal graft is unlikely to be an effective therapeutic surgical agent in the treatment of ulcer. These experiments fail to lend any sup-

port to the thesis that this operation may supplant adequate gastric resection in the management of ulcer.

REFERENCES

1. Stefko, P., Andrus, W., and Lord, J. W., Jr.: The Effects of Jejunal Transplants on Gastric Acidity, Science **96**: 208, 1942.
2. Andrus, W., Lord, J. W., Jr., and Stefko, P.: Comparative Effects of Gastroenterostomy and Pedicle Jejunal Graft on the pH of the Gastric Mucosa, Proc. Soc. Exper. Biol. & Med. **52**: 99, 1943.
3. Lord, J. W., Jr., Andrus, W., and Stefko, P.: Comparative Effects of Pedicle Grafts From Different Levels of Intestinal Tract on pH of Gastric Mucosa, Proc. Soc. Exper. Biol. & Med. **52**: 100, 1943.
4. Lord, J. W., Jr., Andrus, W., and Stefko, P.: Effects of Jejunal Transplants on Experimental Production of Peptic Ulcers, Arch. Surg. **46**: 459, 1943.
5. Andrus, W., Lord, J. W., Jr., and Stefko, P.: Effects of Pedicle Grafts of Jejunum in the Wall of the Stomach on Gastric Secretion, Ann. Surg. **118**: 499, 1943.
6. Andrus, W., Lord, J. W., Jr., Stefko, P., and Dingwall, J. A.: The Effect of Saline Washings of Isolated Jejunal Loops on Gastric Secretion, Am. J. Physiol. **140**: 287, 1943.
7. Andrus, W., Lord, J. W., Jr., and Stefko, P.: A Possible Mode of Action of Pedicle Jejunal Grafts on Gastric Secretion as Indicated by Changes in pH of the Surface of the Mucosa of the Stomach, Am. J. Physiol. **141**: 75, 1944.

AN ATTEMPT TO CONFIRM THE ALLEGED INHIBITORY EFFECT ON GASTRIC SECRETION OF JEJUNAL PEDICLE GRAFTS IN THE WALL OF THE STOMACH

M. I. GROSSMAN, PH.D., M.D., D. F. DUTTON, B.S., AND A. C. IVY, PH.D., M.D., CHICAGO, ILL.

(From the Department of Physiology, Northwestern University Medical School)

IT HAS been clearly established by several groups of workers[1-6] that a piece of jejunum implanted into the wall of the stomach is able to withstand the corrosive action of gastric juice if the vascular pedicle remains intact. These investigators did not, however, report upon the effect of the implants on gastric secretion.

In a series of recent papers,[7-13] Andrus, Lord, and Stefko have reported that the implantation of a pedicle graft of jejunum into the wall of the stomach produces profound effects on gastric secretion. According to their observations, a jejunal pedicle graft implanted in the gastric wall tends to lower the fasting acidity and to reverse the response to histamine injection, that is, administration of histamine to a dog with a jejunal implant in the gastric wall is claimed to depress rather than increase gastric acidity. The stimulatory effect of alcohol on gastric secretion is also reported to be abolished or greatly reduced by these jejunal implants. Ileal and colic transplants into the stomach wall are stated to be ineffective, whereas jejunal transplants are somewhat more effective than duodenal transplants.

The mechanism of inhibition of gastric secretion by jejunal implants has been postulated to be due to a substance formed by the jejunal

Received for publication, Sept. 5, 1944.

mucosa which, when it bathes the gastric mucosa, depresses acid secretion. Thus, saline washings of Thiry loops of jejunum when placed in the stomach of a normal dog and permitted to remain for ten minutes are reported to prevent or greatly diminish the gastric secretory response to histamine injection.

Pedicle jejunal grafts are claimed to be effective both in the prevention and in the cure of experimental ulcers produced in dogs by the prolonged administration of histamine in beeswax.

The operation has been applied by the investigators cited to patients with duodenal or marginal ulcer, and favorable immediate clinical results are reported. It is claimed that gastric secretory changes similar to the alterations observed in dogs occur in these patients; however, examination of the protocols presented does not seem to provide complete support for this contention.

Because of the potential clinical and academic importance which these findings possess, we have attempted to confirm and extend them.

EXPERIMENTAL

Part I: The Effect of Jejunal Washings on the Gastric Secretory Response to Histamine.—

A. In our first studies, dogs with vagally denervated pouches of the entire stomach and esophagoduodenostomies were used in order that quantitative data on uncontaminated gastric juice might be procured. Normal dogs under nembutal anesthesia served as a source of jejunal washings, which were prepared in the following manner. The abdomen was opened by a midline incision. Two small incisions were made in the antimesenteric edge of the gut, one in the descending duodenum and the second in the jejunum about fifteen inches below the ligament of Treitz. Glass cannulas were then tied into the upper and lower ends of the segment of bowel betwen the incisions; 30 c.c. of physiologic saline solution were passed through the segment three times, the washings filtered through cheesecloth, and then made up to 50 c.c. with saline solution. Fresh washings were used for each test, that is, the washings from one dog were used for only one test on each pouch dog. All gastric pouch dogs were in the basal state at the beginning of the test as determined by the absence of free HCl in the secretion.

Immediately after collection, the jejunal washings were perfused through the pouch of the entire stomach continuously for twenty minutes by a modification of a method for perfusion of pouches described elsewhere.[14] At the end of the twenty-minute perfusion period the pouch was thoroughly drained and 1 mg. of histamine dihydrochloride* was injected subcutaneously. Samples were then collected every ten minutes for one hour. A series of control experiments in which physiologic sodium chloride solution was substituted for the jejunal washings was also performed. Although samples were collected for one hour after histamine injection, only the values for the first two ten-minute periods are included in the table because Andrus and his associates report that the effect of the jejunal washings has worn off by the end of twenty minutes (Table I).

*Imido, Hoffmann-La Roche, Inc.

TABLE I

THE EFFECT OF PERFUSION WITH JEJUNAL WASHINGS ON THE ACID SECRETORY RESPONSE OF THE TOTAL STOMACH POUCH TO HISTAMINE

DOG NUMBER	SALINE CONTROL						JEJUNAL WASHINGS					
	MINUTES AFTER HISTAMINE						MINUTES AFTER HISTAMINE					
	0-10			10-20			0-10			10-20		
	V	F	T	V	F	T	V	F	T	V	F	T
1	0.5	0.2	0.8	0.5	1.1	1.4	2.0	0.2	3.3	3.2	4.8	5.6
2	1.5	0.5	1.1	4.5	2.9	4.1	3.5	4.8	6.8	4.0	6.0	7.4
3	0.5	0.4	0.8	1.0	0.8	1.6	1.5	0.2	1.0	2.5	5.3	6.4
4	0.2	0.0	0.1	3.5	7.4	8.6	0.4	0.5	0.8	4.0	10.3	11.8
5	0.5	0.7	0.9	3.0	8.5	9.2	0.5	0.8	1.0	4.0	13.9	14.4
6	1.0	0.0	1.0	2.5	1.2	3.0	1.0	0.0	0.4	1.0	0.9	1.1
7	1.0	1.0	2.0	2.5	7.1	8.3	0.5	0.2	0.6	4.0	5.3	6.8
Av.	0.8	0.4	1.0	2.5	4.1	5.2	1.3	1.0	2.0	3.2	6.6	7.6

V, Volume in cubic centimeters.
F, Free acid in milligrams of HCl.
T, Total acid in milligrams of HCl.

Comment.—In no instance did we note any tendency in the direction of reduction in acid secretion following perfusion of the pouch of the entire stomach with duodenal-jejunal washings.

B. In order to eliminate the possibility that the failure of inhibition was due to the lack of vagal innervation in the total gastric pouch, the same experimental procedure was applied to a dog with a Pavlov (greater curvature, wide isthmus, vagally innervated) pouch of the stomach. Six control experiments with saline solution and six tests with duodenal-jejunal washings were performed. The results appear in Table II.

TABLE II

THE EFFECT OF PERFUSION WITH DUODENAL-JEJUNAL WASHINGS ON THE ACID SECRETORY RESPONSE TO HISTAMINE IN A PAVLOV POUCH DOG

NO. OF TESTS	SALINE CONTROL						NO. OF TESTS	JEJUNAL WASHINGS					
	MINUTES AFTER HISTAMINE							MINUTES AFTER HISTAMINE					
	0-10			10-20				0-10			10-20		
	V	F	T	V	F	T		V	F	T	V	F	T
5	1.3	0.7	1.0	1.9	1.2	1.8	5	2.1	0.5	0.7	1.6	2.4	3.2

V, Volume in cubic centimeters.
F, Free acid in milligrams of HCl.
T, Total acid in milligrams of HCl.

Comment.—The results of perfusion with duodenal-jejunal washings in the Pavlov pouch are similar to those with vagally denervated pouches of the entire stomach, there being no evidence of inhibition of acid secretion in either instance.

Part II. Implantation of Jejunal Pedicle Grafts Into Gastric Pouches.—

Andrus and his associates report that implantation of jejunal pedicle grafts into the wall of a Heidenhain or Pavlov type gastric pouch produced prompt healing of ulceration about the external opening of these pouches. These workers present no data on the effect of the jejunal graft secretion in these animals.

We have implanted jejunal pedicle grafts into the gastric pouch of two dogs with vagally denervated entire stomach pouches, one with a Pavlov type pouch, and one with a Heidenhain type pouch. The operative procedure was essentially that described by Andrus and his

associates. In each case animals were used in which the original operation for preparation of the gastric pouch had been performed a number of months or years previous to the implantation of the jejunal graft and on which a large number of control values for response to histamine were available. Following implantation of the jejunal pedicle graft into the pouch wall, histamine tests were performed at intervals of from 10 to 200 days postoperatively. The results of these experiments are set forth in Table III.

TABLE III

PRE- AND POSTOPERATIVE ACID SECRETORY RESPONSE DURING ONE HOUR AFTER HISTAMINE STIMULATION IN GASTRIC POUCH DOGS IN WHICH A JEJUNAL PEDICLE GRAFT WAS IMPLANTED

DOG NUMBER	TYPE POUCH	PREOPERATIVE CONTROL				POSTOPERATIVE TESTS			
		NO. TESTS	V	F	T	NO. TESTS	V	F	T
1	Entire stomach	11	22.4	79.0	86.2	12	32.6	118.0	129.0
2	Entire stomach	14	30.4	95.4	103.9	5	29.0	86.5	94.3
3	Pavlov	4	51.4	200.9	214.2	4	48.0	184.4	196.8
4	Heidenhain	12	22.0	84.2	93.8	6	25.0	96.5	106.1

V, Volume in cubic centimeters.
F, Free acid in milligrams of HCl.
T, Total acid in milligrams of HCl.

The integrity of the jejunal graft was determined in three cases by sacrificing the animals and examining the excised specimens. On the fourth animal the vitality of the graft was verified by exploratory laparotomy.

Comment.—In none of the four animals provided with a jejunal implant in the gastric pouch was a significant decrease in histamine-stimulated gastric secretion noted.

Part III. Implantation of Jejunal Pedicle Grafts Into the Intact Stomach of the Dog.—

Inasmuch as we were unable to find any evidence of inhibition of secretion by jejunal implants or jejunal washings in gastric pouch dogs we proceeded to study the effect of jejunal pedicle grafts in the intact stomach. Six normal mongrel dogs were trained to lie on a soft pad with a small (Rehfuss) stomach tube in place. Starvation for twenty-four hours preceded each test. The gastric residue was removed and the basal secretion collected over a ten-minute period by continuous gentle suction from a glass syringe. One milligram of histamine dihydrochloride was then injected subcutaneously and the gastric secretion collected by continuous suction for one hour, the samples being divided into six ten-minute periods. Three control tests were performed on each dog and then a pedicle graft of upper jejunum was implanted into the gastric wall in the manner described by Andrus and his associates.[11] This consisted in the resection under morphine-ether anesthesia of an area of the anterior wall of the stomach approximately 4 by 6 cm. in size, about midway between the pylorus and cardia, and the implantation into this defect of a pedicle graft of upper jejunum with its circulation intact. This was obtained by isolating a segment approximately 6 cm. in length, which was then opened along its antimesenteric border and sutured into the gastric window with silk. The continuity of the jejunum was restored by end-to-end anastomosis.

TABLE IV

ACID SECRETORY RESPONSE TO HISTAMINE DIHYDROCHLORIDE (1 MG.) BEFORE AND AFTER IMPLANTATION OF JEJUNAL PEDICLE GRAFT INTO STOMACH

(Average of Three Tests Pre- and Three to Five Tests Postoperatively)

	10 MIN. BEFORE HISTAMINE		0-20 MIN. AFTER HISTAMINE			0-60 MIN AFTER HISTAMINE		
	AV. VOL. (C.C.)	AV. FREE ACID (C.U.)*	AV. VOL. (C.C.)	AV. FREE ACID (C.U.)	AV. FREE ACID OUTPUT (mM)†	AV. VOL. (C.C.)	AV. FREE ACID (C.U.)	AV. FREE ACID OUTPUT (mM)
Dog 1								
Preoperative	8	8	23	85	2.0	112	114	12.8
Postoperative	12	50	34	82	2.8	120	120	14.4
Dog 2								
Preoperative	3	0	30	106	3.2	115	137	15.8
Postoperative	13	19	49	79	1.2	140	97	13.6
Dog 3‡								
Preoperative	7	34	38	110	4.2	127	126	16.0
Postoperative	3	5	19	64	3.9	78	88	6.9
Dog 4								
Preoperative	12	4	25	90	2.3	107	114	12.2
Postoperative	3	12	29	65	1.9	124	101	12.5
Dog 5								
Preoperative	8	0	26	68	1.8	92	87	8.0
Postoperative	4	20	34	59	2.0	116	82	9.5
Dog 6								
Preoperative	4	61	15	95	1.4	87	105	9.1
Postoperative	4	53	33	117	3.9	119	116	13.8
Av.								
Preoperative	7.0	18	26	92	2.5	107	114	10.6
Postoperative	7.1	27	33	77	2.6	116	101	11.6

*C. U., clinical units.

†mM, millimols.

‡When this animal was anesthetized and autopsied a partial obstruction was found at the site of the end-to-end anastomosis in the intestine with dilation and hypertrophy above.

Dogs 2 and 3 showed considerable enterogastric regurgitation in some of the tests.

Ten days to 2.5 months after operation three to five histamine gastric analyses were performed on each animal by the same technique as that used in the preoperative controls.

After all analyses were completed, the animals were sacrificed and the stomach immediately fixed in formalin. Histologic sections were prepared to ascertain the condition of the jejunal graft. In every case normal jejunal mucosa was found. The position of the jejunal patch on the anterior gastric wall is demonstrated in the roentgenogram (Fig. 1) showing outpouching of the wall by the barium meal at this point. The size of the jejunal implant is shown in the picture of the gross postmortem specimen of one of the stomachs (Fig. 2).

The averaged results of the preoperative and postoperative tests on each dog are presented in Table IV.

Comment.—The implantation of a jejunal pedicle graft into the intact stomach of the dog produced no consistent and significant decrease in acid secretion in response to histamine.

DISCUSSION

We have repeated the experiments of Andrus, Lord, and Stefko on the effect of jejunal implants in the gastric wall on acid secretion in response to histamine. Our results give no indication of an inhibitory effect.

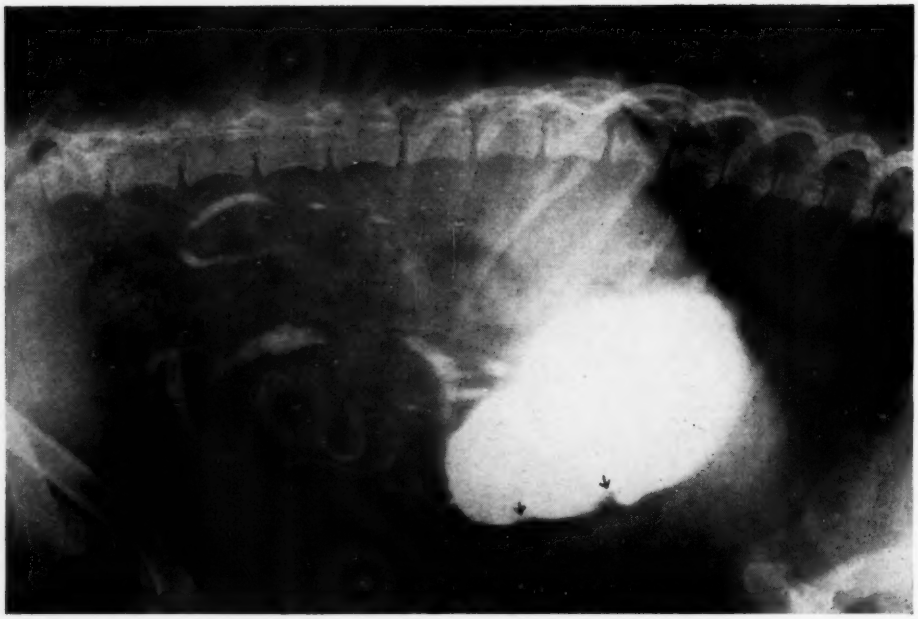


Fig. 1.—Roentgenogram of barium sulfate in the stomach of a dog with a jejunal pedicle graft. The edges of the graft are indicated by the arrows.

Fig. 2.—Photograph of necropsy specimen of stomach with jejunal implant in the fundic area. The scale reads in centimeters.

Perfusion of vagally innervated and vagally denervated gastric pouches with freshly prepared saline washings of the duodenum and jejunum did not affect the acid secretory response to histamine.

Similarly, no decrease in acid secretion in response to histamine was noted in four dogs with gastric pouches into which a piece of upper jejunum was implanted.

In four out of six animals in whom jejunal pedicle grafts were implanted in the wall of the in situ stomach, no significant depression of the secretion of HCl in response to histamine was noted. In the other two animals of this series (Dogs 2 and 3, Table IV) a moderate decrease in the acid *concentration* was noted postoperatively. However, the explanation for the decrease in acid concentration of drainage recovered from the stomach in these two animals was apparent and can be accounted for by the nausea and retching, with regurgitation of bile-stained duodenal contents into the stomach, which not infrequently occurred during the postoperative tests on these animals. However, even in those tests in which enterogastric regurgitation reduced the acidity of some of the samples of gastric contents, the acid values returned to the usual high levels when retching subsided. Furthermore, these two animals in which retching occurred during most of the postoperative tests gave responses as high as the preoperative control values in those postoperative tests in which retching did not take place.

The cause for the increased tendency for retching and enterogastric regurgitation after histamine injection in certain dogs after the operation of jejunal pedicle graft is not obvious.

In only one animal (Dog 3, Table IV) did a decrease in both volume and acid concentration occur postoperatively. It is of interest to note that when the animal was sacrificed a partial obstruction of the bowel due to overgrowth of scar tissue at the site of end-to-end jejunal anastomosis was found in this dog. From prior experience in the performance of many end-to-end anastomoses in the dog, we have found that this occurs in approximately one out of thirty dogs. The possible significance of this finding in relation to the depression of gastric secretion in this animal is conjectural, although it is known that vomiting inhibits the secretory response to a meal and histamine.

It is particularly noteworthy that although the average volume and average concentration show moderate variation between preoperative and postoperative values, the total output of acid (volume times concentration) is not markedly altered.

Andrus and his associates studied gastric secretion for only twenty minutes after histamine injection. Inasmuch as only about one-fourth of the total secretory response to 1 mg. of histamine occurs in the first twenty minutes we have carried out our tests to one hour. It is to be emphasized, however, that even in the twenty-minute period following histamine injection we noted no significant depression of gastric secretion after the operation of jejunal implantation.

The question arises: If, as postulated from the observations of Andrus, Lord, and Stefko, the jejunum did secrete into its lumen a substance which on bathing the gastric mucosa inhibited gastric secretion, what could be the function of such a substance in normal physiologic economy? One could comprehend the function of such a substance

if it were secreted into the duodenal juice which has ready access to the stomach through the mechanism of enterogastric regurgitation. However, according to their observations, jejunal implants are more active than duodenal.

We are unable to suggest a possible cause for the discrepancies between our results and those of Andrus and his associates.

SUMMARY

Implantation of a jejunal pedicle graft into the wall of the stomach or perfusion of the stomach with jejunal washings does not significantly alter the acid secretory response of the stomach to histamine stimulation in the dog.

The authors wish to express their gratitude to Mr. Sam Baker and Dr. Jean Rea Wooley for their assistance in certain phases of this work.

REFERENCES

1. Marie, P., and Villandre, C.: J. de physiol. et de path. gén. **15**: 602, 1913.
2. Mann, F. C.: J. Med. Research **35**: 289, 1917.
3. De Takats, G., and Mann, F. C.: Ann. Surg. **85**: 698, 1927.
4. Morton, C. B.: Ann. Surg. **85**: 879, 1927.
5. Morton, C. B.: Ann. Surg. **87**: 401, 1928.
6. Dragstedt, L. R., and Vaughn, A. M.: Arch. Surg. **8**: 791, 1924.
7. Stefko, P., Andrus, W., and Lord, J. W., Jr.: Science **96**: 208, 1942.
8. Andrus, W., Lord, J. W., Jr., and Stefko, P.: Proc. Soc. Exper. Biol. & Med. **52**: 99, 1943.
9. Lord, J. W., Jr., Andrus, W., and Stefko, P.: Proc. Soc. Exper. Biol. & Med. **52**: 100, 1943.
10. Lord, J. W., Jr., Andrus, W., and Stefko, P.: Arch. Surg. **46**: 459, 1943.
11. Andrus, W., Lord, J. W., Jr., and Stefko, P.: Ann. Surg. **118**: 499, 1943.
12. Andrus, W., Lord, J. W., Jr., Stefko, P., and Dingwall, J. A.: Am. J. Physiol. **140**: 287, 1943.
13. Andrus, W., Lord, J. W., Jr., and Stefko, P.: Am. J. Physiol. **141**: 75, 1944.
14. Butler, D., Hands, A. P., and Ivy, A. C.: Am. J. Physiol. **139**: 3, 1943.

THE INDICATIONS FOR OPERATION IN CASES OF PEPTIC ULCER FROM THE INTERNIST'S POINT OF VIEW

ARTHUR L. BLOOMFIELD, M.D., SAN FRANCISCO, CALIF.

(From the Department of Medicine, Stanford University School of Medicine)

THAT articles on various aspects of ulcer of the stomach and duodenum continue to appear in large numbers indicates, perhaps, that some of the problems are not capable of final solution. Certainly most of the questions about peptic ulcer are not to be answered by exact methods; they remain matters of opinion and hence there are often strong differences among doctors as to matters of procedure. In a symposium published seven years ago in this Journal, I expressed my views[1] on the indications for operation in uncomplicated peptic ulcer. On re-reading that article I see no reason to alter greatly what was said; indeed it would be tedious to review exactly the same material. However, it may be of interest to surgeons, who will make up the bulk of the readers of the present symposium, to have the point of view of a "nonoperating" doctor on some of the indications for surgical interference.

Received for publication, July 17, 1944.

Obstruction.—Pyloric obstruction has been regarded by most physicians as an indication for surgical treatment whether by gastroenterostomy or pyloric resection. It is interesting, therefore, to find a recent article in a surgical journal in which this point of view is questioned.[2] However, few will believe that those instances of vast dilation of the stomach associated with masses of scar tissue which throttle the pylorus can be dealt with by means other than surgical. It is in the borderline cases that nice decisions have to be made. The point is best brought out by considering the reversible and irreversible elements which enter into the production of clinical pyloric stenosis. Scarring and anatomic narrowing can hardly be altered but inflammation of the mucous membrane with edema and spasm, so often associated with fibrous stenosis and acting as a last straw to render the obstruction complete, are usually amenable to treatment. Hence, one may see surprising remissions in patients who at first seemed in a desperate plight. It will rarely be necessary to do an emergency operation and the situation should be reevaluated after a trial period of medical therapy. The following plan has worked well in our clinic: The stomach is emptied by washing with many liters of normal saline solution using a large (Ewald) tube. The procedure must be thorough if the final dregs of retained material are to be reduced to a minimum. The washing is repeated each evening for several days during which the patient is maintained by parenteral alimentation with glucose, saline solution, and, if necessary, some form of protein digest.[3] After two to four days it is usually found that the volume of residual secretion has decreased to less than 100 c.c., and that fluids are passing through in the pylorus. Further proof of this may come from the regurgitation of bile through the duodenum into the gastric washings. One may now begin to feed small amounts of concentrated liquid nourishment during the day but the stomach should still be thoroughly washed each night several hours after the last feeding. This procedure controls stasis and allows the stomach to regain its tone while edema and spasm subside and the pyloric lumen widens. Next it is necessary to decide whether the results have been good enough to justify continued medical treatment or whether operation is necessary. General clinical improvement, roentgen examination of the stomach with umbrathor to show the irreducible degree of obstruction and stasis, the patient's desire or ability to cooperate in a long-time medical regimen, his economic means, his age, and the availability of the best surgical skill all enter into the making of a difficult decision. It is our feeling, however, that if any doubt exists at this point about the success of medical therapy, operation should be done.

Hemorrhage.—Debate as to when one should operate for hemorrhage from peptic ulcer will probably always go on because in the end it comes down to judgment in the individual case and no formula based on statistical experience is entirely satisfactory. Most internists, however, would subscribe to the following propositions: A single bleeding from peptic ulcer in a young person, even if the bleeding is large, rarely kills, and medical treatment is usually satisfactory. The availability of blood and red blood cell concentrates for transfusion is comforting to the doctor under these conditions. In elderly people, on the other hand, severe bleeding, especially if persistent, with the possibility of erosion of a calcified vessel in the base of the ulcer is much more likely

to demand surgical interference. At any rate, every case of this sort should be followed jointly by internist and surgeon, and operation should be done if the bleeding gains headway in spite of transfusion. The internist should remember the surgeon's troubles—a patient usually in poor condition, a stomach full of blood, the difficulty of locating the lesion, especially if in the duodenum, and finally the technical complexities of operation under these conditions.

Another indication for operation is, of course, the occurrence of repeated persistent bleeding over a long period of time even though there never is a threat of exsanguination.

The whole subject has been ably discussed by Heuer[4] in his recent book which is based on a study of carefully collected cases and not on vague impressions. We are in agreement with Heuer that, regardless of theory, a period of fasting for the first few days after a big bleeding is usually safer than feeding.

Ulcer and Cancer.—In the past, one of the strongest reasons for excising a gastric ulcer has been fear lest it should become malignant. That such malignant transformation commonly occurs was generally believed and debate centered only on the exact frequency. Recently the pendulum has swung to the other extreme. The work of Mallory[5] and others[6] on "carcinoma in situ" which shows that cancers may exist in the stomach for long periods without much change before ultimate rapid growth takes place, and the clinical studies of Palmer,[7] have thrown doubt on the frequency of "cancer ex ulcere." These observations tend to show that the usual situation is in fact ulceration in a cancer already present and not cancer developing in an old ulcer. It would seem unreasonable, however, as pointed out by Heuer, to adopt too extreme a position. It is well known that cancer may arise in old leg ulcers, in pulmonary cavities, in brief in many situations where chronic ulceration exists and one surely cannot say that cancer will never develop in a gastric ulcer.

But even if one assumes that cancer is not likely to arise it is often difficult to say whether an "ulcer" when first discovered is benign or is in fact an ulcerated cancer. Here the gastroscope and modern roentgenography are, of course, very helpful but we believe the rule still holds good that any ulcer of the stomach which does not show definite signs of healing after three weeks of careful treatment should be dealt with surgically because of the possibility of cancer in disguise. Even then, one may be misled by apparent improvement of a lesion which is fundamentally cancerous (Eusterman).[8]

Intractable Indigestion.—In a discussion in the previous symposium[1] we sustained the thesis that intractable symptoms even in the absence of bleeding, obstruction, or perforation were an indication for operation. We still believe that position to be sound in many cases. However, one should point out that there has been a shift in emphasis in the whole philosophy of peptic ulcer and indigestion in the past few years, especially as a result of war experiences,[9] and this may alter one's attitude toward surgical indications. Peptic ulcer, in brief, has been definitely brought into the domain of psychosomatic medicine. The interesting observations of Draper,[10] the important work of Wolf and Wolff[11] which amplifies with modern methods what Beaumont saw a hundred years ago, and the clinical studies of innumerable internists and psychiatrists[12]

have shown beyond question the important part which psychologic influences play not only in promoting symptoms, but also through the mechanism of spasm and hyperemia in actually causing the breakdown of tissue. The position seems so securely established that most patients probably deserve technical psychiatric consideration before being subjected to operation. In different cases, however, either the psychic or the somatic component may predominate. If the psychogenic factor is prominent one should be cautious about operation; if such factors seem inconsequential, operation to excise a scarred and irritable duodenal cap and break up indigestion reflexes by creating a wide stoma is, we believe, sound practice even if no bleeding or obstruction exists.

Two patients seen recently illustrate the point: Both had long-standing indigestion; spastic deformed duodenal caps were shown by x-rays; both had responded to hospital therapy but relapsed under their usual activities. Neither had bled or shown signs of obstruction. In one no psychogenic material could be brought out; he agreed in a matter-of-fact way to any sort of interference if it would give relief. The second patient yielded a mine of trouble on psychiatric study; his symptoms were done away with not by operation but by a stay in the psychiatric ward.

SUMMARY

Many of the problems of peptic ulcer are not capable of solution by exact methods; they remain matters of opinion upon which physicians will differ. The points brought out with reference to indications for operation may be summarized briefly as follows.

What at first appears to be total pyloric stenosis may in fact be partly due to reversible spasm and edema. Hence, operation should rarely be done until measures to relieve such spasm and edema have failed.

From the surgical standpoint the great problem of hemorrhage is to recognize that it has become "intractable" before it is too late to save life by operation. Since a first hemorrhage in a young person is rarely fatal one may put off operation longer than in an elderly person with persistent bleeding. Transfusion of concentrated red blood cells may be lifesaving in preparing a patient who has bled severely.

Cancer develops so rarely in gastric ulcer that prophylactic excision is not usually indicated. However, ulcers apparently benign which fail to heal promptly may in fact be cancer and should be removed by gastric resection.

With the recognition that peptic ulcer is often a psychosomatic problem, operation will be done less often than formerly for indigestion (without obstruction or hemorrhage), but operation still has a place in refractory cases with insignificant psychiatric symptoms.

REFERENCES

1. Bloomfield, A. L.: The Indications for Operation in Cases of Uncomplicated Peptic Ulcer, SURGERY 2: 710, 1937.
2. Hinton, J. W.: The Intractable Duodenal Ulcer: Evaluation of Surgical Procedures, Ann. Surg. **117**: 498, 1943.
3. Altschuler, S. S., Sahyun, M., Schneider, H., and Satriano, D.: Clinical Use of Amino Acids for the Maintenance of Nitrogen Equilibrium, J. A. M. A. **121**: 163, 1943.
4. Heuer, George J., Holman, Cranston, and Cooper, William: The Treatment of Peptic Ulcer, Philadelphia, 1944, J. B. Lippincott Company.

5. Mallory, Tracy B.: Carcinoma in Situ of the Stomach and Its Bearing on the Histogenesis of Malignant Ulcers, Arch. Path. **30**: 348, 1940.
6. Palmer, W. L.: Duration of Cancer of the Stomach, Gastroenterology **1**: 723, 1943.
7. Palmer, W. L.: See discussion in Portis, Sidney A.: Diseases of the Digestive System, Philadelphia, 1941, Lea & Febiger, p. 511.
8. Eusterman, G. B.: Carcinomatous Ulcer, J. A. M. A. **118**: 1, 1942.
9. Dunn, W. H.: Gastroduodenal Disorders: An Important Wartime Medical Problem, War Med. **2**: 967, 1942.
10. Draper, G.: The Emotional Component of the Ulcer Susceptible Constitution, Ann. Int. Med. **16**: 633, 1942.
Draper, G., and Touraine, G. A.: The Man-Environment Unit and Peptic Ulcer, Arch. Int. Med. **49**: 616, 1932.
11. Wolf, S., and Wolff, H. G.: Evidence on Genesis of Peptic Ulcer in Man, J. A. M. A. **120**: 670, 1942.
12. Mittlemann, B., and Wolff, H. G.: Emotions and Gastro-duodenal Function, Psychosom. Med. **4**: 5, 1942.

THE MEDICAL TREATMENT OF PEPTIC ULCER REFRACTORY TO SIPPY THERAPY*

ASHER WINKELSTEIN, M.D., ALBERT CORNELL, M.D., AND FRANKLIN HOLLANDER, PH.D., NEW YORK, N. Y.

(From the Gastro-Intestinal Division of the Medical Department and the Gastroenterology Research Laboratory, The Mount Sinai Hospital)

THE entire etiology of peptic ulcer is as yet unknown. However, no matter what the ultimate cause may be, there is no doubt that the "acid-pepsin factor" is the immediate agent of the ulcerative process. There is considerable evidence to support this view. For example: (1) Peptic ulceration occurs only in areas exposed to active gastric juice, that is, the lower part of the esophagus, the stomach, the upper third of the duodenum, the jejunum (following gastroenterostomy), and Meckel's diverticulum (when it contains parietal cells). (2) Peptic ulcer does not occur in the presence of a complete achlorhydria (as proved with histamine and neutral red). (3) Recurrent ulceration is prevented by gastric resection when this operation results in an achlorhydria. Conversely, marginal jejunal ulcers may occur when the acid is not eliminated.

On the other hand, there exists a considerable number of predisposing and aggravating factors without some of which peptic ulcers cannot be formed even by a highly potent gastric juice. Among these must be included the following: (1) emotional upsets which cause certain localized circulatory disturbances, prolonged gastric retention, and excessive and prolonged gastric secretion (especially during the night); (2) diminished tissue resistance associated with inadequate nutrition, circulatory disturbances, toxic infectious processes, and inadequate mucous secretion; (3) motor effects in the stomach, such as spasm, hypermotility, and atony; (4) impaired neutralization of acid gastric chyme by decrease of mucus, mucoid secretion, or duodenal

Received for publication, Nov. 2, 1944.
*This work was carried on in part with the support of John Wyeth and Brother, Inc.

regurgitation of bile, pancreatic secretion, and intestinal secretion; (5) certain endocrine influences; (6) postoperative states, such as gastroenterostomy and partial gastrectomy with persistent free acidity; (7) miscellaneous factors, including excessive use of alcohol or tobacco, food irritants, extensive burns, constitutional factors.

It must be emphasized that, despite all the arguments in favor of the acid-pepsin theory of ulcer formation, no valid claim can be made that this factor stands out as "the specific cause" of peptic ulcer disease. Rather, active gastric juice must be considered as the agent by which the lesion itself is produced in a stomach normally impervious to its action, but which is made susceptible to such ulceration by suitable predisposing factors. Ample evidence for this is afforded by the fact that perhaps 75 per cent of all patients with gastric ulcer and 20 per cent of those with duodenal ulcer have low or normal acidities, whereas some individuals manifest typical hypersecretory curves *without* objective evidence of ulceration. The occurrence of peptic ulcer in patients with normal or low gastric acidity appears to present a contradiction, but it may be explained by considering ulceration as the result of *peptic* digestion rather than acid irritation.[1]

In view of our inability to control adequately the predisposing factors, it has become the aim of most current therapeutic procedures, medical and surgical, to eliminate the immediate agent of tissue destruction, the "acid-pepsin factor." The most common examples of such procedures entail the following: (1) antispasmodics (for example, atropine) to lessen the retention of gastric secretion; (2) alkalies, to neutralize the hydrochloric acid; (3) high-fat diets, to inhibit acid secretion; (4) frequent feedings, to absorb and dilute the acid; (5) sedatives to inhibit the nervous secretion of acid and pepsin; (6) gastric aspiration, to remove excess retained gastric juice; (7) partial gastrectomy, to reduce the output of acid and pepsin; (8) gastroenterostomy, to increase the neutralization of acid by duodenal regurgitation; (9) surgical vagotomy, to lessen the output of both acid and pepsin in the psychic phase of secretion.

Chronic peptic ulcer is a lifelong disease and only a small percentage of patients are cured medically, while a fair percentage go through life with mild symptoms. The remainder, about 25 per cent, are refractory and require intensive medical or surgical therapy. For this purpose, the usual Sippy therapy seems inadequate, because it does not control the acidity between the meals. Studies from this hospital reveal that there is a very high secretion of acid during the night,[3, 4] even while the patient is on Sippy treatment during the day. Frequent Sippy feedings may in themselves serve as an added stimulus to the nervous phase of acid secretion and may not allow sufficient functional rest, motor or secretory. Other disadvantages of Sippy therapy are as follows: (1) The diet is nutritionally deficient and is increased too slowly. (2) It necessitates an in-bed routine, either in the hospital or the home. (3) Remissions after Sippy treatment are short, and recurrences are often severe. (4) The large amount of absorbable alkalies used may lead to a harmful systemic alkalosis in the presence of renal dysfunction. (5) It does not constitute an adequate means of effecting interdigestive neutralization, especially of the night secretion.

Various other methods have been used to control the harmful nocturnal hypersecretion, usually before retiring, but they are also often ineffective. These include gastric aspiration, atropine, sedatives, olive oil, alkalies given separately or in combination. As a result of the failure of these measures to control the symptoms associated with the night secretion, there arose the idea of *continuous intragastric drip therapy throughout the twenty-four hours.*[2] As originally introduced, this treatment was defined as a "local intubation ulcer therapy based on the principle of a continuous, adequate, intragastric neutralization of the free hydrochloric acid between the meals and during the night by a milk-soda drip." With the advent of nonabsorbable alkalies in 1934, various preparations of aluminum hydroxide and phosphate gels were included in the drip treatment.[5] These colloids, besides preventing alkalosis, are antipeptic and astringent, and can be substituted for the milk-sodium bicarbonate mixture wherever the latter is contraindicated, as in cases of an allergic reaction or an idiosyncrasy toward milk. However, the nutritive value of milk and the simplicity of the apparatus required for its administration favor its use whenever conditions permit. A mixture of milk and alumina gel has also been tried and found adequate.

Physiologic evidence regarding the value of intragastric drip therapy was established by a series of studies which showed the efficacy of the method in reducing gastric acidity.[6] With both the milk-sodium bicarbonate and aluminum hydroxide or aluminum phosphate gels, an average nocturnal, interdigestive pH of 1.4 was elevated to a mean pH of 3.5 to 4.0, thus inducing a harmless achlorhydria between the meals and during the night. At this higher pH, about 90 per cent of peptic activity is also eliminated. Hence, the continuous drip procedure affords a method for the continuous neutralization throughout the twenty-four-hour cycle, thus achieving the sina qua non of ulcer healing, namely, a continuous achlorhydria.[7]

An experience of thirteen years with the continuous intragastric drip method has demonstrated the clinical efficacy of this most recent advance in the medical therapy of peptic ulcer. Certain practical points in the application of this therapeutic procedure may be noted:

1. The technique is learned quickly so that nearly all the patients can administer it to themselves at home during the night. Individuals in our outpatient group are often unable for economic reasons to discontinue their daily routine, and enter the hospital whenever they have a severe recurrence. Using a vessel similar to the ordinary enema can as a milk container, and a Murphy drip indicator, they can operate the drip at home during the night and carry on their work during the day, thus continuing a "home cure" for as long as may be necessary.

2. Most of these patients are "tube broken," having had various gastric analyses performed upon them, so that they do not find the method drastic or difficult. With the recent introduction of the latex tube[8] instead of the semirigid Levin tube, patients are able to use the drip over long periods of time without distress. Whichever tube is employed, the patient is taught to pass the tube on himself so that he does not have to depend on a nurse or doctor. The details of the drip therapy technique have been fully described elsewhere.[9]

3. Moderate and severe cases require the drip between the meals as well as during the night, whereas mild cases require it only during the night.

4. Continuous twenty-four-hour drip therapy is rarely necessary; usually, it is reserved for patients with intractable pain, during the first twenty-four or forty-eight hours, and especially for those with nocturnal pain.

5. Three liberal bland "ulcer" meals are given, preceded by atropine and phenobarbital, and followed with aluminum gel. This regime, in combination with the interdigestive drip, permits adequate tissue nutrition and provides an optimal neutralization.

6. There is usually a rapid loss of symptoms, sometimes after only twenty-four hours.

7. Ulcer niches heal rapidly, and huge craters in the stomach have sometimes been found to disappear in less than three weeks, as proved by x-ray and gastroscopy. We have seen many very long remissions after this form of therapy, which is particularly significant in view of the refractory type of patient receiving this treatment.

8. It is the best method of controlling the distressing night symptoms of ulcer, without disturbing the patient's sleep.

9. It has helped avoid surgical therapy in a considerable number of cases. In fact, it is our opinion that no patient with uncomplicated ulcer should be operated upon until drip therapy has first been tried.

10. Large gastric ulcers, at first thought to be malignant, have sometimes been proved benign by the rapid diminution in size and the loss of symptoms, thus aiding in the differential diagnosis.

11. Should operation ultimately be decided upon after the intragastric drip therapy, the lesion will be found more easily resectable because of its smaller size and the decreased inflammation.

The ulcer patients who were refractory to the usual Sippy treatment and who subsequently responded to drip treatment, either with milk-soda or aluminum gel, in this hospital, now total about sixty. This group includes: elderly men with penetrating ulcers of long duration with short or no remissions; patients with uncontrollable night pains; individuals with recurring massive hemorrhage, usually treated surgically; patients who could not be treated surgically because of age and poor general condition, or who refused surgery; and those with unyielding, severe pains during the day. Ordinarily a group of refractory ulcer patients like these would be considered candidates for surgical therapy. As a result of the application of the continuous intragastric drip therapy, however, they lost their symptoms and showed objective evidence of healing of the lesion. That other clinics have had similarly good results with this mode of treatment is indicated by a recent statement of Eusterman's,[10] that "the superiority of the drip method over conventional procedures is unquestionable, especially in the treatment of the more refractory lesions." Consequently, we are presenting detailed case reports on twenty-two of these sixty patients, chosen as representative of the entire group, in order to illustrate the successful application of this form of therapy to such refractory cases. It is hoped that this will stimulate the further study of therapeutic procedures along these lines.

ALUMINUM HYDROXIDE OR PHOSPHATE GEL DRIP CASES

CASE 1.—F. W. was a woman, aged 42 years. In 1929, x-rays revealed evidence of duodenal ulcer. Because of severe epigastric pain, anorexia, vomiting, and loss of twelve pounds, the patient was admitted in 1940 to The Mount Sinai Hospital. The present attack of four weeks' duration was unrelieved by the usually controlling dietary measures and Sippy regime. Free acid was 75mN (millinormal), total 90mN. The patient became entirely symptom-free on the aluminum phosphate drip for three weeks during the night and between meals. In addition to the duodenal deformity, gastrointestinal x-rays showed a small diverticulum of the second portion. A Rehfuss test was done after drip therapy; free acid was 40mN, total 56mN. The patient has done well for four and one-half years without any serious recurrence.

CASE 2.—F. D. R. was a man aged 38 years. The patient had a fifteen-year history of duodenal ulcer when admitted in 1940 for "intractable pain." There was a history of tarry stools in 1937, treated at another hospital. In the one and one-half weeks before admission, he had epigastric and back pain with loss of eight pounds and suffered night pain not relieved by Sippy therapy. Although surgery was strongly advised, he preferred medical treatment. He received the aluminum phosphate drip between meals and nightly for three weeks with relief of symptoms. Gastrointestinal series now showed duodenal irregularity with slight six-hour residue. He has been followed since in the out-patient department and continues well on diet and medication after four and one-half years.

CASE 3.—J. G. was a man, aged 36 years. The patient was admitted in 1940, with a ten-year history of heartburn, one hour after meals, relieved by soda. In the one and one-half years before admission he had epigastric pain, nausea, vomiting, back pain, anorexia, and loss of sixty-five pounds. For the last three weeks, pain was persistent with no response to milk or alkali, and night pain was a prominent feature. Gastroscopy revealed a large, irregular gastric ulcer on the lesser curvature, extending from the anterior to the posterior surface with a nodular base, suspicious of malignancy. Free acid was 90, total 115mN. The patient received the continuous aluminum hydroxide drip at night and between meals for two and one-half weeks. Pain disappeared and the patient's condition was definitely improved coincident with the use of the drip. On repeating the gastroscopy, the ulcer was one-third the original size, superficial and healing, and appeared definitely benign. Gastrointestinal x-rays failed to show the penetrating ulcer crater previously seen. The idea of surgery, considered at first, was dropped. The patient was followed in the outpatient department in 1942, and was well on ambulant regime.

CASE 4.—V. P. was a man, aged 49 years. The patient, with a two-year history of epigastric pain, complained of extremely severe and continuous pain in the two days before admission with radiation to the back and loss of thirteen pounds in the past five weeks. He failed to be relieved by Sippy treatment. He was admitted with marked direct and rebound epigastric tenderness. Gastrointestinal x-ray series revealed a gastric ulcer, five-eighth inches in size, on the posterior wall near the re-entrant angle on the lesser curvature. Gastroscopy showed a deep ulcer, three-quarter inches in diameter, benign in appearance. Because the lesion was possibly malignant, aluminum phosphate drip was advised, although surgery was considered seriously. He received the drip between meals and at night for about three weeks, after which gastroscopy showed ulcer only one-quarter inch in size, benign and healing. Surgery was not considered further, and he has been followed since in the outpatient department and is doing well, over two and one-half years after the drip therapy.

CASE 5.—W. R., a man, aged 32 years, entered the hospital in April, 1940, with a seven-year history of gnawing epigastric pain. X-rays showed a duodenal ulcer shortly after onset. Free acid was 94, total 110mN. Because of a three months' attack of severe pain unrelieved by Sippy therapy, he was placed on aluminum phosphate drip, between meals and nightly for three weeks, with rapid improvement and subsidence of pain and tenderness.

CASE 6.—S. D. was a woman, aged 43 years. The patient was admitted in October, 1940, with a six months' history of epigastric pain, worse in the past two months, when pain radiated to the back, usually at night. Sippy treatment failed to help the patient. She then received the aluminum phosphate drip for twelve days between meals and nightly. Free acid was 80, total 110mN, before drip treatment. This was reduced to a free acidity of 12mN, with no acid in six specimens after the drip. X-rays proved the presence of a duodenal ulcer. The patient improved definitely and was relieved of pain coincident with the use of drip therapy.

CASE 7.—R. R., a man, aged 53 years, was admitted November, 1940, with tarry stools, weakness, and dizziness for three days before admission. This was the patient's third hemorrhage in the past six years. He had been on Sippy therapy for several weeks before the hemorrhage. Evidence of bleeding with guaiac positive stools lasted one week. He received the aluminum phosphate drip day and night for over two weeks, with cessation in bleeding and steady improvement after the first week. The patient has remained well for two years. He was last seen in the middle of 1942.

CASE 8.—G. M. was a man, aged 62 years. This patient had ulcer symptoms for twenty years. Ten years before admission he was operated on for an acute perforation of the ulcer. He remained well for a short period (two months) and then the symptoms recurred severely. For seven months he suffered from ulcer pains, particularly at night. He was treated in the hospital for four weeks with strict Sippy therapy. However, the night pains and pain and heartburn after meals persisted. X-ray examination revealed two rather large ulcer niches in the duodenal bulb. There was a high gastric acidity (80mN). He was treated with aluminum phosphate gel drip with a rapid loss of symptoms. He continued the drip at night at home for eight weeks. X-ray examination then revealed only a deformity of the bulb. The niches had disappeared. He has remained in perfect health since then, a period of two years.

MILK AND ALUMINUM GEL DRIP CASES

CASE 1.—M. R., a man, aged 27 years, with a five-year history of duodenal ulcer, entered the hospital because of tarry stools. A second attack of melena occurred one year later. Free acid was 120, total 130. Operation was strongly urged, but refused. His third admission was in December, 1941, with a history of tarry stools and pain. Whereas formerly he had been treated with Sippy therapy, he was now given the aluminum hydroxide drip for nine days and milk drip for one week, day and night. Gastrointestinal series showed deformity of duodenal bulb with a small posterior wall crater. The patient has remained well for over three and one-half years with no recurrence of pain or bleeding.

CASE 2.—I. S. was a man, aged 57 years. The patient had a thirty-five year history of peptic ulcer, with pain after meals and at night. Eight years before, tarry stools were passed, and subtotal gastrectomy was advised at that time, but refused. On the present admission, free acid was 98, total 110mN, and a radiograph showed a deformed bulb. Sippy therapy was discontinued and he was placed on the milk drip day and night for twelve days and the aluminum phosphate drip for six days. Marked relief, disappearance of pain, and increased appetite were obtained. Follow-up: After four years, the patient continues to do well.

CASE 3.—E. W. was a woman, aged 38 years. The patient had a two-year history of epigastric pain and a particularly severe attack in the two months before admission, requiring a hypodermic of morphine for relief of back pain. X-rays in the outpatient department one week before revealed a penetrating gastric ulcer. Gastroscopy showed a deep ulcer, 2.5 cm. on the posterior wall and lesser curvature of the stomach. When Sippy therapy failed to relieve her, she was started on the aluminum gel drip between meals and after one week received the milk drip during the day and night for two weeks. The patient was slow at the start to show improvement and surgery was considered. However, she continued with marked improvement, subsidence of pain, and gain of over ten pounds in weight. Follow-up x-rays showed a complete disappearance of the ulcer.

MILK DRIP CASES

CASE 1.—S. S. was a man, aged 42 years. After one year of typical ulcer symptoms, a severe gastric hemorrhage occurred. Three weeks later, an x-ray examination revealed a large penetrating ulcer at the angle. There was a high acidity (60mN). He was treated for six weeks with a strict in-bed Sippy therapy. Another series of radiographs showed that the ulcer was unchanged. Surgical therapy was then considered for a possible neoplasm. However, milk-soda drip was tried first. After four weeks of drip therapy, the niche had completely disappeared. He then continued the drip therapy at night for several more weeks. After that he was asymptomatic for one and one-half years. He then died suddenly from a heart attack. The autopsy revealed a scar of a healed lesser curvature ulcer.

CASE 2.—C. C., a man, aged 40 years, had severe ulcer symptoms for one and one-half years. He was then on Sippy therapy for two months. A moderately severe hemorrhage then occurred and the hemoglobin fell to 55 per cent. Radiographs revealed an ulcer niche in the duodenum. He was treated for three weeks with the milk-soda drip. He continued the drip only at night for one year. He has remained well with normal radiographs for nine years.

CASE 3.—I. H., was a man, aged 20 years. During the previous two years the patient had had four severe attacks of ulcer symptoms. On the fifth attack, a duodenal ulcer and a small gastric ulcer at the angle were demonstrable in the radiographs. Despite the strictest Sippy therapy, the symptoms grew worse and surgical therapy was advised. However, it was decided to try milk-soda drip therapy first. He was given the drip following meals and during the night. He lost the symptoms in forty-eight hours. After leaving the hospital, he continued the drip therapy in the College Infirmary at night through the college year. Three months after the institution of the drip therapy, radiographs revealed a normal stomach and duodenal bulb. This patient has remained in perfect health for three and one-half years.

CASE 4.—A. F., a man, aged 47 years, had typical ulcer symptoms for ten years, including a massive hemorrhage. For three months, he suffered with severe ulcer symptoms unrelieved by Sippy therapy and foreign protein injections. Radiographs then revealed an ulcer niche in the stomach at the angle. The free acidity was high (75mN). He was then treated with the milk-soda drip. He lost the symptoms in twenty-four hours and the niche disappeared in three weeks. He remained well for three years. A slight recurrence, with negative x-rays, was relieved by one week of drip therapy. He has remained well for two years.

CASE 5.—A. Z. was a woman, aged 45 years. After a few weeks of severe ulcer symptoms, the patient had a severe gastric hemorrhage. She was treated with transfusions and Sippy therapy. She was well for six weeks. Then ulcer symptoms of a severe nature returned. X-rays showed a duodenal ulcer. Despite three weeks in bed on strict Sippy regime, her condition grew steadily worse. A moderate degree of pyloric obstruction appeared. She was then treated with the milk drip (without soda) for four weeks. She lost all of her symptoms and has remained well for five years.

CASE 6.—J. C., a man, aged 68 years, had ulcer symptoms for six years. For the six months before admission he was on Sippy therapy without relief. Radiographs revealed a large ulcer niche at the gastric angle. Milk-soda drip was then administered for four weeks. Radiographs then revealed an absence of the niche. He has remained well for eighteen months and has gained twenty pounds.

CASE 7.—L. B., a man, aged 57 years, had a twenty-three year ulcer history. A gastroenterostomy was done twelve years before admission for an obstructing duodenal ulcer. He remained well thereafter for eleven years. During the past year, he had severe ulcer symptoms, despite strict Sippy therapy. In fact, while on treatment, he experienced two massive hemorrhages. X-rays revealed a large jejunal ulcer opposite the stoma. He was then treated in the hospital with milk-

soda drip for two weeks and at home for four weeks. Radiographs then showed a disappearance of the niche. He has remained well to the present time (nineteen months).

CASE 8.—M. J. was a woman, aged 48 years. After three years of ulcer symptoms, radiographs revealed a prepyloric niche. The free acidity was high (70 mN). Despite four weeks of intensive, in-bed strict Sippy therapy, the symptoms continued. Vomiting and pain were excessive, especially during the night. She was then given the milk-soda drip. She lost the symptoms in two days and the niche in three weeks. She has gained eight pounds and remained well to the present (ten months).

CASE 9.—L. S., a man, aged 67 years, had ulcer symptoms for thirty years. A gastroenterostomy was performed seventeen years before admission. He remained well for sixteen years. He then developed severe ulcer symptoms and a large, penetrating jejunal ulcer was found opposite the stoma. He was treated for two months with Sippy therapy without relief. He then took the milk-soda drip for four weeks in the hospital and for four months more at home at night. Two months after the onset of the drip therapy, radiographs revealed an absence of the niche. He has remained well for nine years and has gained fifty pounds.

CASE 10.—M. S., a man, aged 44 years, had ulcer symptoms for eleven years. The symptoms became quite severe in the past four months. Despite Sippy therapy he had severe night pains. He was given twenty-four injections of histidin without result. Radiographs revealed a large ulcer niche at the incisura angularis. The free acidity was high (60mN). He was then given the milk-soda drip for four weeks. Radiographs then showed that the niche had disappeared. He has remained well to the present (seventeen months).

CASE 11.—G. R. was a man aged 38 years. After one year of typical ulcer symptoms, the patient experienced a severe hemorrhage from a duodenal ulcer. The symptoms continued despite six weeks of Sippy therapy. He was then treated with the milk-soda drip for three weeks. He lost the symptoms in twenty-four hours. He continued the drip at home for another three weeks. Radiographs which had revealed just before the drip therapy a tiny, deformed bulb, now showed an almost complete bulb. He has remained well for three and one-half years.

SUMMARY AND CONCLUSIONS

1. The chief point of attack in peptic ulcer therapy is the "acid-pepsin" factor.

2. The usual forms of ulcer therapy, including the Sippy method, are reviewed and their inadequacies are discussed.

3. The principles of the intragastric drip therapy for peptic ulcer are described.

4. A group of sixty ulcer patients, refractory to the usual medical therapy, were treated with milk-soda or aluminum gel by the intragastric drip procedure. Twenty-two of these are presented as examples of the successful application of this form of therapy to refractory peptic ulcer patients.

REFERENCES

1. Hollander, Franklin: What Constitutes Effective Neutralization of Gastric Contents? Am. J. Digest. Dis. **6**: 127, 1939.
2. Winkelstein, Asher: Studies in Gastric Secretion During the Night With a Preliminary Note on a New Therapy for Peptic Ulcer, Am. J. Surg. **15**: 523-524, 1932.
3. Winkelstein, Asher: One Hundred and Sixty-Nine Studies in Gastric Secretion During the Night, Am. J. Digest. Dis. **1**: 778-782, 1935.
4. Cornell, Albert, Winkelstein, Asher, and Hollander, Franklin: Nocturnal Secretion Studies in Normals and in Patients With Peptic Ulcer, Bull. New York Acad. Med. **20**: 413, 1944.

5. Woldman, E. E., and Rowland, V. C.: A New Technique for the Continuous Control of Acidity in Peptic Ulcer by the Aluminum Hydroxide Drip, Am. J. Digest. Dis. 2: 733-736, 1936.
6. Cornell, Albert, Hollander, Franklin, and Winkelstein, Asher: The Efficacy of the Drip Method in the Reduction of Gastric Acidity, Am. J. Digest. Dis. 9: 332-338, 1942.
7. Cornell, Albert, and Hollander, Franklin: An Improved Continuous Drip Apparatus With Special Reference to the Use of Alumina Gels in the Therapy of Peptic Ulcer, Rev. Gastroenterol. 9: 354-358, 1942.
8. Woldman, E. E.: A Collapsible Indwelling Nasogastric Tube, Am. J. Digest. Dis. 4: 428-429, 1937.
9. Winkelstein, Asher, Cornell, Albert, and Hollander, Franklin: Intragastric Drip Therapy for Peptic Ulcer—A Summary of Ten Years' Experience, J. A. M. A. 120: 743-745, 1942.
10. Year Book of General Medicine, Chicago, 1943, The Year Book Publishers, Inc., page 632.

THE TREATMENT OF PERFORATED DUODENAL ULCERS

ROSCOE R. GRAHAM, M.B., TORONTO, CANADA, AND
MAJOR E. B. TOVEE,* ROYAL CANADIAN ARMY MEDICAL CORPS

IN A former communication[1] were presented the details of the management of a series of fifty-one consecutive patients with perforated duodenal ulcers who had been admitted to the First Surgical Division of the Toronto General Hospital. The present communication includes this group together with a further series totaling 114 consecutive patients admitted to the same surgical service over a period of fifteen years since July 1, 1929. We wish to stress that this communication deals with perforated duodenal ulcers, and excludes from consideration perforated gastric ulcers. This we consider wise for two reasons: first, the number of perforated gastric ulcers which we have had the opportunity to treat has been very small, and second, a considerable proportion of these were malignant. It was felt that their inclusion in this study would but confuse the problem. We propose to confine our presentation of the management of the emergency created by the perforation of a duodenal ulcer, leaving the subsequent fate of the patient for a further communication.

All but three of the 114 patients in this series were submitted to operation. There were ten deaths. All three patients not operated upon died. Of these three, one patient refused operation. The second patient refused, and later consented, but died in the operating room before surgery could be undertaken. We failed to make a diagnosis in the third patient until the autopsy was performed. This showed a perforation of the duodenum which had localized as a left subphrenic abscess, with the terminal factor being a rupture into the bronchus. The patient drowned in his own pus.

There were seven operative deaths in 111 operations, a mortality of 6.3 per cent. There were forty-nine consecutive operations without a death. The fiftieth patient died of a pulmonary embolus on the twelfth

[1] Received for publication, Sept. 8, 1944.
*Resident Surgeon, Toronto General Hospital, temporarily on loan from the Canadian Army overseas.

TABLE I

Total cases perforated duodenal ulcer	114	Died 10
Total cases operated upon	111	Died 7 (6.3%)

Cause of death in three nonoperated patients
- 2 refused operation
- 1 undiagnosed (perforated a subphrenic abscess into bronchus)

Cause of death in 111 patients operated upon
- 1 pulmonary embolus
- 1 pneumonia
- 1 pneumonia with senility
- 1 pneumonia with mild peritonitis
- 1 uremia
- 1 unrecognized pelvic abscess which perforated into the general peritoneal cavity
- 1 subphrenic abscess ruptured into bronchus

day after operation. The second death was due to pneumonia. At autopsy the abdomen was free from infection. The third patient died from pneumonia and at autopsy there was a mild peritonitis with no leak from the site of the omental patch. It was felt that pneumonia was the major factor in the mortality. The fourth patient, on the twelfth postoperative day, developed uremia and died from this cause. The fifth patient died from an unrecognized pelvic abscess, which ruptured into the general peritoneal cavity. The sixth patient died from a subphrenic abscess which was unrecognized postoperatively until it ruptured into the bronchus. The seventh patient, a senile man who could not be kept in bed, developed pneumonia and died from this cause three weeks postoperatively. He had recovered from the operation.

The ratio of males to females is striking, there being 107 male as opposed to 7 female patients in this group. Sixty-four patients were under and fifty were over 50 years of age. There were as many deaths in patients under as over 50 years of age. We cannot, therefore, consider the age of the patient as being a very important factor in determining the incidence or mortality of this emergency. The age of the patients varied from 16 to 83 years. The average age of the whole group of patients was 47 years.

Most of these patients were operated upon by the resident surgeon or the senior intern. Fortunately, the interval between the onset of symptoms and the operation has been quite short in most instances. This reflects very admirably on the efficiency of the general practitioner in this area, and furthermore it shows the wisdom of not transporting over long distances patients suspected of having a perforation. The best surgeon to operate upon a patient with a perforated duodenal ulcer is the surgeon on the spot. In no case in which we have operated has the patient made a journey longer than twenty-five miles. This was at variance with the experience in a similar group of cases in one of our Veterans' Hospitals, where the patients have been transported long distances before operation was undertaken, with a much higher mortality.

The diagnosis in most instances has presented very little difficulty. The commonest mistakes which we have made have been to diagnose erroneously as an acute perforation of a duodenal ulcer, cases of acute appendicitis, acute hemorrhagic pancreatitis, and, on a rare occasion,

acute cholecystitis. We have very rarely made a diagnosis of a perforated ulcer when the patient actually had acute appendicitis. We have had patients admitted with the diagnosis of a perforated duodenal ulcer who were proved to be suffering from coronary thrombosis. To date we have not submitted to operation any patient with the diagnosis of a perforated duodenal ulcer who was subsequently found to have a coronary occlusion. The diagnosis of a perforated duodenal ulcer in the female must always be made after very careful consideration, since it occurs so infrequently that all other possible diagnoses should be carefully assessed before concluding that the patient has this lesion. This incidence parallels the rarity of calculus cholecystitis in the unmarried nulliparous female.

In the vast majority of this group there was a previous history of indigestion, and in the patients who had this previous history there was almost invariably a history of an acute recent exacerbation of the symptoms varying in length from a few days to two or three weeks prior to perforation. There were a few cases in which it was impossible to elicit a previous history of duodenal type of gastrointestinal distress. In this group of patients the findings at operation were different from those of the group who presented a history of prolonged indigestion. There was found to be little scarring, the ulcer often presenting a punched-out appearance with very minor periperforation induration. Such we believe to result from an acute ulcer, possibly metastatic from remote infection.

The physical examination is of tremendous importance in making the diagnosis. One of us[2] previously outlined a trinity of symptoms regarded as indicative of an intraperitoneal catastrophe. These are: (1) the association of abdominal pain with tenderness, (2) one point of maximum tenderness, and (3) increase of pain on change of posture such as occurs when the patient rolls over in bed. In other words, if a patient complains of pain in the right iliac fossa and is tender in the area where the pain is felt, we conclude that the lesion is intraperitoneal. Such are the findings in acute appendicitis. On the other hand, if the patient complains of pain in the right iliac fossa but is not tender to palpation there, we believe the lesion is extraperitoneal, such as a ureteral stone producing colic. If one adds to this trinity the presence of rebound tenderness on abdominal examination, we accept this as irrefutable evidence of an intraperitoneal catastrophe, demanding a laparotomy.

We have never seen a case of perforated duodenal ulcer without a leucocytosis. One must recognize a physiologic leucocytosis such as may be found, for example, in the premenstrual phase in women. One must be on guard during the period of reaction from the onset of the acute pain. During this time we may find the patient reasonably comfortable with a normal temperature and a normal pulse. We may be lulled to a sense of false security and fail to recognize the emergency. Abdominal rigidity, however, is almost always present in some degree.

When the physical examination, together with the leucocyte count and urinalysis, has been carried out, the patient is taken to the x-ray laboratory and screened for the purpose of detecting the presence of air under the diaphragm. This finding is of great diagnostic value. If one

can demonstrate the presence of free air in the peritoneal cavity, it is pathognomonic of an intraperitoneal perforation. We must not, however, diagnose the presence of free air in the peritoneal cavity solely on the absence of liver dullness. We have seen instances in which the liver dullness was obliterated by distended colon. Thus, while the finding of air under the diaphragm and the absence of liver dullness are of tremendous value in diagnosis of a perforated duodenal ulcer, failure to obtain these signs conversely is definitely no deterrent to this diagnosis. Indeed, in no instance in the last seven patients with perforated ulcer which we operated upon was air demonstrable underneath the diaphragm. Shoulder-tip pain, when present, is of real diagnostic value, as it indicates diaphragmatic irritation from some cause.

Having established the diagnosis, we must ask ourselves several questions. First, why is the patient with the acute perforation of a duodental ulcer sick? The answer to this question which would be given by many, and indeed which we believed for some time, was, that bacterial peritonitis was the factor responsible for the patient's illness. This, however, has been refuted by our studies of bacteriology of the peritoneal exudate in these patients. In fifty-nine patients cultures were taken from the peritoneal cavity at the time of operation. Thirty-four of these fifty-nine cultures yielded no growth. Of the twenty-five which showed organisms on culture, there was one instance of pure culture of typhoid bacilli in a patient who twenty years previously had suffered from typhoid fever.[3] There were only two instances in which colon bacilli grew on culture. There was only one case in which there was a growth of hemolytic streptococci. This occurred in a 49-year-old man with a twelve-hour perforation, who had a perfectly uneventful convalescence and whose peritoneal cavity was closed without a drain. The other instances in which a positive culture was found included nonpathogenic organisms such as nonhemolytic streptococci, streptococcus viridans, diphtheroid bacilli, and staphylococcus albus, the latter probably being a contamination. We must, therefore, look farther afield than the peritonitis which accompanies this emergency to explain why these patients are sick. In consideration of this problem we concluded that the seriousness of the patient's emergency was in direct ratio to: (1) the degree and duration of his pain, (2) the extent of his biochemical imbalance, and (3) the degree of nutritional disturbance present.

As was mentioned before, in the great majority of these patients there had been a previous history of indigestion with a recent acute exacerbation of their symptoms. Many of them had an inadequate nutrition of long standing for one of three reasons: First, they would not eat a proper diet because of some erroneous preconceived idea; second, they were unable to retain it; third, they were never properly advised regarding the necessity and details of an adequate diet. We have been very impressed with the soundness of the conception that the nutritional disturbance of the patient at the time of the perforation is a very important factor in contributing to the seriousness of their emergency. The aphorism which has been so often quoted that, "The sun must never rise and the sun must never set on a patient suffering from an acute perforation of a duodenal ulcer without such a patient being operated upon," we believe to be thoroughly unsound. Our ex-

perience with this further group of patients has led us to believe more firmly in the wisdom of correcting the patient's nutritional disturbance and biochemical imbalance before operation is undertaken. This has, on occasions, occupied as long as twelve hours after the patient's admission to the hospital. We have never found such delay to be disastrous.

Case 1 is interesting in this connection.

CASE REPORT

CASE 1.—A man, aged 53 years, was admitted to the department of medicine for the investigation of an indigestion of which previous studies had failed to show evidence of organic disease. He had complained bitterly on many occasions of abdominal pain, and had had many previous operations. At 6 A.M. he suffered a sudden epigastric pain with diffuse tenderness and rigidity. He was seen in consultation six hours later. Screening showed no free air under the diaphragm. He appeared to be desperately ill, his blood pressure being 70/50. The diagnosis of a perforated viscus presented little difficulty. The condition of the man, however, was so poor that immediate operation was considered unwise. He was put in an oxygen tent, was given sufficient sedative to relieve the pain, and was given an intravenous injection of saline solution and glucose, as well as 500 c.c. of plasma and 500 c.c. of whole blood, all intravenous medication being by the drip method. His condition improved and at the end of ten hours his blood pressure was 110/76 and pulse was 80. His appearance and general condition were in marked contrast to his state when first seen. Interestingly enough at operation, which revealed a perforated duodenal ulcer, cultures from the intraperitoneal exudate were sterile. Despite the fact that operation was not undertaken until sixteen hours following the perforation, ten hours being consumed in preoperative preparation, he made an uninterrupted recovery. We are convinced that in this case immediate operation would have ended fatally.

One may ask, what are the criteria for deferring operation? This can be summed up in an assessment of the patient's general nutrition, the state of dehydration, the blood pressure, pulse rate, and temperature. We have never regretted the time consumed in the preoperative preparation of the desperately ill patient. Furthermore, in this group of 114 patients, in which there were 7 operative deaths, there were only 3 instances in which the peritoneal infection was a contributing factor to the fatality. There were two subphrenic abscesses which ruptured into the bronchus, one of which was not diagnosed until autopsy. The third patient had pneumonia with an early mild peritonitis and the pneumonia was considered to be the major factor responsible for the fatality.

The next three questions we must ask ourselves are: (1) Why is an emergency operation ever necessary in gastrointestinal disease? (2) What is the surgeon's responsibility in an emergency operation on the gastrointestinal tract? (3) Upon what do we depend for the closure of gastrointestinal perforation? These three questions must be answered in order to undertake the operative procedure intelligently and adequately.

In answering the first it must be obvious that we do an emergency operation solely because we believe that without operation the patient would die. In answering the second, the surgeon's responsibility in an emergency operation is solely to save life, and to do that with the most simple, minimal, surgical procedure which will accomplish this end. The third answer is that all gastrointestinal perforations are closed by the formation of fibrin. This makes possible all intestinal anastomoses.

The perforation made by each stitch is soon healed by fibrin. Our problem is to ensure fibrin formation at the site of the perforation.

With this conception of our responsibility in an emergency operation, we can consider the anesthetic. We are firmly convinced that the use of a spinal anesthetic is ideal. There have been instances when the patient was so desperately ill that this anesthetic seemed injudicious. With increasing experience, however, the contraindications are decreasing. We used local block anesthesia in the abdominal wall, plus splanchnic block anesthesia transperitoneally in the patients who were too ill for spinal anesthesia. The patient enters the operating room with a Levin tube in the stomach and an intravenous infusion of glucose and saline solution already running. The intravenous therapy is useful not only for immediate value, but to provide a medium whereby stimulants may be given effectively and readily should the need become urgent during the operation. We recently have been using sodium pentothal as a supplement to spinal anesthesia to overcome any apprehension and restlessness on the part of the patient.

If the diagnosis is in doubt, and it is impossible to determine whether the patient is suffering from acute appendicitis or a perforated ulcer, the peritoneal cavity is opened through a gridiron incision in the right iliac fossa. This results in a minimum trauma. If the appendix is the source of the trouble it is effectively dealt with, whereas if the appendix is normal the upper abdomen may then be opened by a separate incision. Fibrin may be present around the appendix in the right iliac fossa, although the original lesion is a perforated ulcer. One must be on guard to recognize that such is a periappendicitis and not a primary appendicitis. To be alert to this possibility is sufficient to avoid an error. In our opinion it is much less traumatic to approach the doubtful case in this manner than it is to make a more extensive paramedian laparotomy wound as the primary procedure.

If there is no doubt as to the diagnosis, the abdomen is opened through the upper right rectus muscle and the perforation usually is readily found by following the fibrin toward the duodenal cap.

Accepting the philosophy that we have no responsibility except to save the patient's life, we are spared any debate as to whether we should do a concomitant gastrojejunostomy, pyloroplasty, or gastric resection. None of these procedures is necessary to save the patient's life. Some may argue during the operation for acute perforation that the degree of scarring and induration at the site of the perforation makes pyloric obstruction inevitable. The operative procedure we suggest will not add to the mechanical obstruction which antedated the perforation. The patient presented no emergency problem because of pyloric obstruction prior to the perforation, thus any aggravation of the pyloric stenosis is due to edema resulting from the acute inflammatory process accompanying the perforation. This can be controlled by using an indwelling duodenal tube with Wangensteen suction, maintaining by parenteral means adequate nutritional and biochemical balance. In the few cases in which this proves inadequate, a jejunostomy may be simply and safely done as an operation of election. This permits complete study of the patient and the performance of an adequate gastric operation at the optimum time. We cannot too heartily condemn all procedures save simple closure at the operation for the acute perforation.

We have at this time no responsibility whatsoever to attempt to cure the patient of his duodenal ulcer. Realizing also that fibrin is responsible for the closure of all perforations in the gastrointestinal tract, we guide fibrin to the perforation in the most simple manner possible. Three interrupted catgut sutures are placed parallel to the long axis of the duodenum, one above, one below, and one across the perforation (Fig. 1). We then lay over the perforation a piece of omentum, either attached or detached, whichever seems the less disturbing to the intraperitoneal content, and then tie the sutures just sufficiently tight to hold the omental patch in position (Fig. 2). The sutures are not tied tight enough for an attempt to be made to close the perforation. They

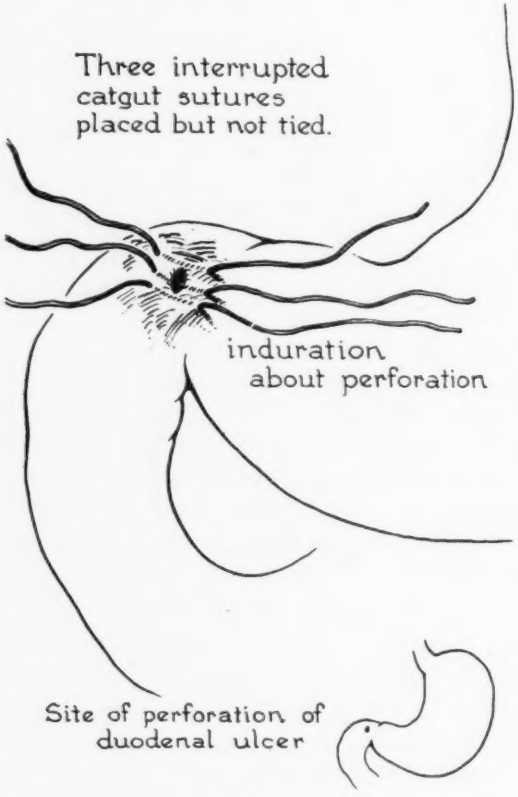


Fig. 1.

Fig. 2.

Fig. 1.—The placing of sutures in relation to perforation.

Fig. 2.—Sutures tied over free omental graft. No attempt is made to close the perforation by the sutures. They are tied only sufficiently tight to hold the graft in situ.

simply hold the omentum over the perforation so that fibrin forms in this area. If there is gross soiling of the peritoneal cavity, the exudate is sucked out, but one should not be so insistent upon sucking out all the intraperitoneal fluid as to traumatize the intraperitoneal contents unnecessarily. The abdominal wall is then closed without drainage, according to one's practice. Closure with stainless steel wire as advocated by Jones and associates[4] we believe is admirable. The elimination of drainage has become almost routine. Unless there is gross contamination in a very late perforation it serves no useful purpose. In ninety-eight cases in which the presence or absence of drainage was definitely stated, a drain was left in at the time of the original operation in only fourteen. We have not used any of the sulfonamide drugs rou-

tinely in the peritoneal cavity. In this entire group there were only three cases in which a sulfonamide was left in the peritoneal cavity.

On the patient's return to the ward, if his condition is grave, he is placed in an oxygen tent and given sufficient sedative, preferably morphine, to control his pain. The intravenous administration of saline solution and glucose is maintained, and the stomach is kept empty by aspiration of the indwelling duodenal tube. We then carry on with the postoperative routine suggested by one of us[5] for gastric operations. The patient's position is changed every two hours and he is encouraged to exercise the legs. Overbreathing is stimulated by the administration of carbon dioxide every two to four hours for the first twelve hours postoperatively and he is encouraged to cough.

If the patient is not doing well, there are three areas which must be examined immediately: first, the chest; second, the subphrenic spaces; and third, rectal. A rectal examination would have avoided the disaster which occurred to us when an unrecognized pelvic abscess perforated into the general peritoneal cavity and caused a fatality. There is one pitfall in the investigation of the subphrenic spaces. If the patient has been operated upon under spinal anesthesia, and his unsatisfactory postoperative course leads one to suspect the presence of a subphrenic abscess, x-ray studies which show free gas under the diaphragm must not be taken as evidence in the support of a subphrenic lesion. Lewis[6] has shown in a series of cases that air will normally occupy the subphrenic space in patients who have had a laparotomy under spinal anesthesia for as long as six weeks following operation. In our hospital, as reported by Doidge and Warner,[7] the diagnosis of a subphrenic abscess requires all the resources at our disposal and despite these we fail all too frequently.

Before the patient is discharged from the hospital a careful survey is made for possible sources of infection in the teeth, tonsils, and accessory sinuses. Advice is given, in writing, detailing the management of his life and diet. We believe it is much more important for a patient to eat a varied diet between meals and at bedtime, as well as the three main meals, than it is to go on any elaborate and detailed and curtailed diet. We also insist on the value of avoiding the use of alcohol or tobacco in any form.

A further communication will deal with the subsequent fate of these patients, the incidence of postoperative symptoms, and the necessity for subsequent operation.

SUMMARY AND CONCLUSIONS

1. A series of 114 perforated duodenal ulcers is presented. One hundred and eleven patients were operated upon with seven operative deaths, a mortality of 6.3 per cent. In only three patients did an intraperitoneal infection contribute to the fatality.

2. The factors responsible for the seriousness of this emergency are: (a) the degree and duration of the pain, (b) the degree of biochemical imbalance, and (c) the degree of nutritional disturbance.

3. The preoperative treatment of the patient is the most important factor in lowering the operative mortality, despite the necessity of deferring the operation on occasion for as long as twelve hours.

4. Bacterial peritonitis as a factor in the seriousness of this emergency is a late manifestation. In fifty-nine cultures, thirty-four were sterile. In only two cases were colon bacilli found on culture. Hemolytic streptococcus was recovered once and a pure culture of typhoid once. The other positive cultures contained nonpathogenic organisms. These findings justify withholding operation while biochemical and nutritional disturbances are corrected.

5. The routine use of sulfonamide drugs intraperitoneally appears superfluous.

6. Drainage of the abdomen at the time of closure of the perforation is unnecessary.

7. Under spinal anesthesia the closure of the perforation by an omental patch, attached or detached, held in place by three interrupted catgut sutures is an efficient and simple method. This reduces operative trauma and technical difficulties to the minimum and can be carried out with safety despite limited facilities.

REFERENCES

1. Graham, R. R.: Treatment of Perforated Duodenal Ulcers, Surg., Gynec. & Obst. **64**: 235-238, 1937.
2. Graham, R. R.: Surgical Emergencies in General Practice Exclusive of Trauma, Canad. M. A. J. **34**: 36-40, 1936.
3. Clifford, E. J.: Perforated Duodenal Ulcer in Typhoid Carrier, Canad. M. A. J. **28**: 194-195, 1933.
4. Jones, T. E., Newell, E. T., Jr., and Brubaker, R. E.: The Use of Alloy Steel Wire in the Closure of Abdominal Wounds, Surg., Gynec. & Obst. **72**: 1056-1059, 1941.
5. Graham, R. R.: Technical Surgical Procedures for Gastric and Duodenal Ulcer, Surg., Gynec. & Obst. **66**: 269-287, 1938.
6. Lewis, F. I.: Pneumo-peritoneum Following Laparotomy, Canad. M. A. J. **28**: 18-23, 1933.
7. Doidge, W. A., and Warner, W. P.: Subphrenic Abscess, SURGERY **4**: 405-414, 1938.

EXPERIMENTAL EVALUATION OF A SATISFACTORY OPERATION FOR ULCER

B. G. LANNIN, M.D.,* MINNEAPOLIS, MINN.
(From the Department of Surgery, University of Minnesota)

INTRODUCTION

I. Purpose of the Present Study

OF ALL the theories that have been advanced regarding the etiology of ulcer, the majority of investigators now recognize acid as the most important single factor. Whereas it has been known for some time that ulcer might be produced by various surgical procedures which alter the normal anatomy, only recently has it been possible to produce

The researches presented here were supported by grants of the Citizens Aid Society, and the Augustus L. Searle Fund for Experimental Surgical Research.

*In partial fulfillment of the requirements for the degree of Doctor of Philosophy, May, 1944.

typical chronic duodenal and gastric ulcers in a variety of intact laboratory animals.

It thus becomes apparent that an operative procedure, which would protect an animal against the development of such an experimentally induced ulcer, would have considerable clinical value in the surgical therapy of ulcer in man where similar lesions occur spontaneously.

It is the purpose of this study then, to evaluate several operative procedures, experimentally, and determine which one or ones would have satisfactory clinical application.

II. Review of the Literature

The voluminous accumulated literature attests to the widespread interest which the ulcer problem has initiated.

Countless means and methods have been employed in an attempt to reproduce the clinical lesions in experimental animals.

It should be stated initially that the difference between the acute and chronic ulcer has long been appreciated. Morton[83] stated that, "the means of inducing chronic ulcer in animals, experimentally, are as few as those of inducing acute ulcer are numerous." Whereas an acute ulcer may be produced by a variety of methods, almost invariably it is found to be entirely healed within two or three weeks. It was not until the work of Mann and Williamson[76] (1923) that a method was made available of producing chronic ulcers consistently in a high percentage of animals.

Although, as has been mentioned, the methods previously employed have been quite numerous and varied, an attempt will be made to classify them, give examples of each group, and discuss a few of them somewhat more in detail.

A. Methods Altering the Normal Anatomy and Physiology of the Alimentary Tract, Especially the Normal Capacity for Neutralization, the Chemical Factor.—Bickel[10] (1909) excised the duodenum in two dogs and established continuity by gastrojejunostomy. He implanted the bile and pancreatic ducts into the abdominal wall as external fistulas. At autopsy, after four and one-half weeks, one of the animals showed several jejunal ulcers, one of which perforated with resulting peritonitis and death. Exalto[35] (1911) observed no ulcer in seven dogs with gastroenterostomy. However, of seven dogs upon whom the Roux Y operation was performed, six subsequently developed ulcer. He stated that jejunal ulcers were due to the action of the acid gastric juice on the intestinal mucosa. Because of his findings, he condemned the Roux Y operation and indicated that the operation least likely to be followed by jejunal ulcer was a posterior gastroenterostomy performed as close as possible to the duodenum. These observations were quite remarkable as they are certainly true today, nearly thirty-five years later.

Grey[42] (1919) performed duodenectomy in dogs in multiple stages. At the first stage the common bile duct was ligated and the gall bladder anastomosed to the proximal jejunum. At the second stage, the major pancreatic duct was transplanted into the proximal jejunum and finally the duodenum was resected and the upper jejunum was anastomosed to the stomach. However, of four animals surviving the

second stage, two subsequently died before the final procedure could be accomplished. At autopsy, both animals were found to have perforated peptic ulcers—one in the distal duodenum and the other in the first inch of jejunum, above the transplanted pancreatic duct. He concluded that the ulcers were due to the absence of the strongly alkaline juices ordinarily present in this region.

Mann and Kawamura[75] (1922) studied the effects of duodenectomy. Of ten animals coming to necropsy, two showed typical jejunal ulcers. The following year (1923) Mann and Williamson[76] described their operation of "surgical duodenal drainage" in which the alkaline duodenal secretions are shunted into the terminal ileum. Fourteen of sixteen dogs developed typical subacute or chronic jejunal ulcers. Mann ascribed this occurrence to a chemical and a mechanical component. He emphasized the significance of unneutralized gastric acid and the "nozzlelike" action of the pylorus which allowed the gastric secretion to come in contact with the duodenal mucosa in spurts with considerable force.

Mann and Williamson's work was widely recognized and confirmed by a number of investigators. Following this, numerous studies were undertaken to determine which of the duodenal secretions, the bile, pancreatic juice, or succus entericus provided the greatest neutralizing capacity for the acid gastric juice.

Dott and Lim[29] (1923) noted typical jejunal ulcers in dogs after gastroenterostomy with pyloric exclusion as suggested by Von Eiselsberg,[109] but did not note them in gastroenterostomy without pyloric exclusion. They therefore concluded that acid chyme was necessary to stimulate the alkaline secretions of the duodenum including the bile and pancreatic juice, and that with deficient alkaline secretion, ulcer would result. These findings are quite interesting and will be discussed later, somewhat more in detail.

Dragstedt and Vaughn[30] (1924) attempted to answer the age-old question of "why the stomach does not digest itself." They implanted various segments of intestine, spleen, and kidney into the stomach but failed to note any evidences of digestion. They concluded that the immunity to resist gastric digestion was more general than was formerly supposed and did not reside wholly in mucous membranes. They suggested that the hypothesis that all living uninjured cells could resist digestion was partly true.

Kapsinow[58] (1926) accomplished total exclusion of bile by ligating the common duct and performing cholecystonephrostomy. He succeeded in producing typical duodenal ulcer in seventeen of forty-three animals and, therefore, concluded that bile was an important factor in neutralization.

De Takats and Mann[26] (1927) transplanted 5 cm. jejunal loops and sutured them as patches into the stomach wall. A typical peptic ulcer occurred in three of twenty-five animals when the patch was placed along the lesser curvature; they did not occur if the patches were placed elsewhere in the stomach. They felt that this finding added significance to the mechanical factor in the formation of ulcer.

Morton[83] (1927) confirmed the findings of de Takats and Mann and continued the investigation. He produced acute ulcers in the stomach

by excising segments of the mucosa and submucosa and noted that all healed in normal fashion. He then excised small areas of the mucosa and performed the Mann-Williamson operation coincidentally. A delay in healing resulted in all experiments, and 50 per cent of the ulcers on the lesser curvature became subacute or chronic, whereas similar areas on the greater curvature healed.

In another series of experiments he performed the duodenal drainage operation. After an interval of twenty to sixty-five days, the animal was again operated upon and the presence of a jejunal ulcer confirmed. A gastroenterostomy was performed at this laparotomy. The animals were then sacrificed in from four to sixteen days. All ulcers showed unmistakable evidences of healing. However, newly developing ulcers were found opposite the gastroenteric stoma.

Somewhat later Morton[84] placed jejunal patches in various locations on the stomach, as suggested by Mann, and noted only one ulcer. He then did the operation of duodenal drainage in thirteen animals. Of five dogs with the patches on the lesser curvature, typical ulcer developed in three instances. Otherwise, no ulcer occurred and it thus appeared that the lesser curvature was the most susceptible location.

McCann[69] (1929) altered the Mann-Williamson operation by implanting the duodenal loop high in the fundus of the stomach, thus assuring complete intragastric regurgitation. Jejunal ulcers were found in 80 per cent of twenty-six dogs following this procedure. He also studied the gastric secretion following the procedure and the Mann-Williamson operation. No significant change in the acidity of the secretion resulted and he therefore assumed that the jejunal ulceration was due to a failure of neutralization of the normal acid chyme rather than a hyperacid secretion.

Neuman, Demoor, and Deloyers[85] (1931) noted ulcers in four of seven dogs with total exclusion of bile into the terminal ileum. With deviation of duodenal and pancreatic secretions, ulcers were obtained in two of six dogs. Loewy[68] also produced duodenitis and ulceration with total external biliary fistulas. Berg and Jobling[8] (1930) noted chronic duodenal ulcers in thirteen of twenty-three dogs with various types of biliary exclusion.

Elman and Hartmann[33] (1931), however, emphasized the importance of the pancreatic juice and noted ulcers in six dogs with pancreatic fistulas which drained for thirteen days or more. Berg and Zucker[9] (1932) again, on the contrary, re-emphasized the importance of the bile and noted ulcers in 60 per cent of animals with biliary exclusion and only one ulcer in fourteen animals with pancreatic fistula. In a later report, Berg[7] (1934) found only one ulcer in sixteen dogs with pancreatic fistula, and no ulcers in eight dogs with total pancreatectomy.

Owings and Smith[90, 91] (1932) also favored the bile as the most important neutralizing factor in preventing ulcer. They performed Mann-Williamson operations but implanted the duodenal loop only twenty-four inches below the gastroenterostomy which had been made a few inches below the ligament of Treitz. In seven dogs in which ulcer developed, they then implanted the proximal loop into the stomach; in four instances the ulcer healed completely, and in two cases partial healing resulted. This would appear to be contrary to McCann's findings.

Jenkins and Palmer[54] (1931) performed Mann-Williamson operations but made a wide side-to-side gastroenterostomy stoma rather than the usual end-to-end gastrojejunostomy. The same incidence of ulcer resulted, however, and they therefore concluded that unneutralized acid was the most important factor rather than the mechanical effect. Later, Gallagher and Palmer[40] (1933) noted no difference in the rate of development of jejunal ulcer in the Mann-Williamson preparation if the duodenal loop was implanted at various levels in the intestinal tract.

Bollman and Mann[12] (1932) found ulcer in sixty-four of eighty-seven dogs with ligation of the common bile duct and Kim and Ivy[60] (1931) noted spontaneous duodenal ulcers in six of ten dogs with biliary fistula.

Mann and Bollman[73] (1932) were able to produce ulcer by dripping 0.4 per cent hydrochloric acid into the stomach through an intestinal fistula and stated that daily repetition of excess acidity was necessary to cause a depression of neutralization.

In a preliminary report, Matthews[78] (1931) noted the effect of anastomosing a Pavlov pouch to an isolated loop of lower ileum. A typical ulcer developed in all instances (six dogs) within eighty days.

Matthews and Dragstedt[79] (1932) furnished considerable evidence for the acid genesis of ulcer. They stated that the results of Dragstedt and Vaughn[30] might be explained by the neutralizing effect of food, swallowed saliva, mucus, and the regurgitation of alkaline duodenal juices. Their "experimental Meckel's diverticulum ulcer" demonstrated convincingly the corrosive chemical action of unneutralized pure gastric juice. They also repeated the Mann-Williamson experiment but implanted the duodenal loop only 40 cm. below the gastrojejunostomy.

Only one ulcer in twenty-one experiments was noted. They then introduced a valve which prevented regurgitation of the duodenal juices, and chronic jejunal ulcers resulted in six cases.

Similarly, the prevention of the regurgitation of the alkaline duodenal juices into the stomach of normal dogs by the introduction of a valve into the pylorus raised the free and total acidity of the gastric content, delayed healing of acute gastric ulcers, and caused the appearance of spontaneous ulcers in intestinal mucosal transplants.

Harper[45, 46] (1932 and 1935) attacked the problem in a slightly different manner but with convincing results. He made fundic pouches in the dog and used antiperistaltic loops of various segments of the intestine to carry the secretion to the outside as described by Mann and Bollman.[74] He found that ulcers formed in the fistulas in all instances. The average interval before perforation when utilizing the ileum was twenty-three days, whereas, with the jejunum the interval increased to seventy-one days. If the duodenum was employed, ulcers developed but perforation did not occur. He thus concluded that the upper intestine is more resistant to the corrosive action of gastric juice than the lower segments. If catheters were introduced through the fistulas into the pouch to assure good drainage, ulceration failed to occur.

Ivy, Schrager, and Morgan[53] noted spontaneous duodenal ulcers in dogs with chronic mild icterus and hepatitis.

Hoerner[49] (1934) studied the effect of exclusion of the pancreatic juice from the duodenum. Following evulsion of the pancreatic ducts, ulcer failed to occur, but with pancreatic fistula, ulcer was observed in 42 per cent of the animals.

No change in the gastric contents was found following either of these procedures but the reaction of the duodenal contents in a fasting state was more variable and after a protein or carbohydrate meal the pH of the duodenal content was lower and maintained for a longer time.

Ochsner, Gage, and Hosoi[87] (1934) convincingly demonstrated the protective influence of bile. They noted an incidence of ulcer in 85 per cent of animals in whom pouches had been anastomosed to the jejunum. However, if the bile was introduced by anastomosis of the gall bladder to the pouch, the incidence of ulcer was lowered to 39 per cent.

Blanck[11] (1935) believed that the loss of bile was of paramount importance in inducing experimental ulceration. He made complete external biliary fistulas in eight dogs. Five were fed only the stock diet and all developed ulcers. The remaining three were fed the bile collected from the biliary fistulas in addition to the stock diet and no ulcers were observed.

Wu[122] (1935) made Mann-Bollman fistulas 5 to 10 cm. below the ligament of Treitz and studied the pH of the intestinal content. He then performed the Mann-Williamson operation and observed that the jejunal contents were much more acid than normal, and subject to wider fluctuations. McMaster[71] (1934) made end-to-side anastomosis between the pyloric end of the stomach and progressively lower levels of the intestine from the duodenum to the colon. The intestinal mucosa was observed to be increasingly sensitive to gastric content from the duodenum to the colon. No ulcers were observed with gastroduodenostomy, a 45 per cent incidence with gastrojejunostomy, an 80 per cent incidence with gastroileostomy, and a 100 per cent incidence with gastrocolostomy. He believed the acid gastric content appeared to be the most important factor in the production of ulceration of the intestinal mucosa. These findings offer opportunity for considerable speculation and will be discussed more in detail later.

DeBakey[25] (1937) attempted to ascertain the relative protective power of the bile, pancreatic juice, and succus entericus. He performed pyloric exclusion and gastrojejunostomy after the method of Von Eiselsberg.[109] He then excluded the bile and pancreatic juice individually and collectively.

With pyloric exclusion alone, ulcer was observed in 50 per cent of the animals; with pancreatic juice excluded, 70 per cent; with bile excluded, 90 per cent; and with both juices excluded, 100 per cent. He, therefore, concluded that bile was of greatest importance in preventing the formation of jejunal ulcer, with pancreatic juice next in order and the succus entericus least important.

Bachrach, Schmidt, and Beazell[1] (1939) observed only two ulcers in fifteen dogs with complete biliary fistulas if the collected bile were returned. In nineteen dogs with pancreas separated from the duodenum, only one ulcer was observed.

Schiffrin[96] (1940) stressed the importance of pepsin and was unable to produce ulcer in an intestinal loop by employing acid alone but succeeded with an acid pepsin mixture.

However, Walpole and his co-workers[110] produced ulcer in the cat by instillation of dilute hydrochloric acid, and Varco[107] succeeded in producing ulcer in a loop of dog's intestine employing acid.

More recently Kolouch,[61] by observing directly the effects of acid on an exposed loop of intestine, has studied the pH necessary to produce ulceration.

In summary, several facts become apparent. The effect of unneutralized gastric acid is undeniable. Mechanical and traumatic factors may play a role but certainly a lesser one. Bile appears to be the most important factor in neutralizing acid, with pancreatic juice next in order and the succus entericus least important. Ulcer may be produced consistently by altering the normal acid-alkaline mechanism. There appears to be a progressive increase in susceptibility to gastric acid from the duodenum to the colon.

B. Methods Altering the Normal Vascular Supply of the Stomach.—Virchow's theory of embolic infarction as the etiologic agent in ulcer stimulated many investigators to attempt to produce ulcer disturbing the normal blood supply to the stomach. The first attempts were the introduction of foreign body particles into the blood stream.

Panum[92] (1862) injected an emulsion of wax into the femoral artery of dogs and produced multiple hemorrhagic infarcts and ulcers in the stomach. However, the majority of the animals died within twenty-four hours, so the fate of the ulcers was inconclusive. Cohnheim[21] (1890) injected a suspension of lead chromate into one of the gastric branches of the splenic artery. He produced large ulcers which were usually perfectly healed at the end of three weeks. Other investigators used a variety of substances with rather variable results. Ivy[52] injected suspensions of finely divided animal charcoal into the gastroepiploic arteries with negative results, but succeeded in producing acute ulcers in three animals by using lead chromate.

The effects of ligation of blood vessels supplying the stomach were also investigated. Litthauer[66] was able to ligate the blood supply of one-third of the stomach without producing ulcer. He then ligated all the vessels in a given area of the stomach, excised a segment of mucosa, and fed the animals 200 c.c. of dilute hydrochloric acid daily. He was able to produce ulcer in two of eight experiments but stated that the "artificial production of a condition of hyperchlorhydria was essential to obtain a true gastric ulcer."

Ivy[52] ligated six to eight of the branches of the gastroepiploic vessels supplying the pyloric portion of the stomach, with negative results. He also made silver nitrate ulcers in areas where the large blood vessels had been ligated and found that they healed in normal time.

Reeves[94] studied the anatomic arrangements of the arteries along the lesser curvature and first portion of the duodenum and noted that anastomoses were infrequent. He suggested that these vessels were predisposed to thrombosis which might be an important factor in the causation of ulcer by hematogenous infection.

Layne and Bergh[64] found that ligation of two or three of the large arteries supplying the stomach produced no significant alteration of acid gastric secretion nor alteration in the appearance of the gastric mucosa. Thus it would appear that alterations in blood supply to the

stomach, which might occur clinically, would be distinctly unusual and most certainly play a minor role as etiologic factors in the production of ulcer.

C. Methods Altering the Normal Nerve Pathways.—A number of investigators have altered the normal nerve pathways in an attempt to produce ulcer. The majority of attacks have been directed at the vagi, the splanchnics, and the central nervous system. Unfortunately, a number of conflicting reports have caused some confusion in this regard, especially the vagi.

Durante[31] (1916) produced ulcer by resecting the splanchnic nerves. He stated that the integrity of the gastric cell was dependent upon the sympathetic nervous system and damage to these structures would cause a "trophic" ulcer. Greggio[41] (1916) was able to produce ulcer in the dog and rabbit by vagotomy. Beaver and Mann[5] (1931) made Mann-Williamson preparations and, in addition, sectioned the vagi in the thorax in one series of animals, and in another, divided the splanchnics. Ulcer developed in all except one instance and they, therefore, concluded that section of these nerves would not prevent the occurrence of ulcer.

Beazell and Ivy[6] found gastric ulcer in twelve of twenty-nine rabbits fed on a rough diet and in whom bilateral vagotomy had been performed. If the animals were fed a soft diet, however, ulcer was observed in only three of nineteen animals. They concluded that mechanical trauma was a factor, therefore. Ulcer did not occur in sixty dogs receiving a soft diet, upon whom bilateral vagotomy was performed above the diaphragm.

Lium[67] (1941) noted peptic ulcers in four of nine dogs upon whom the prevertebral ganglia had been removed.

Oberling and Kalto[86] noted, incidentally, lesions of the stomach in twelve of twenty-nine animals after operations upon the central gray nuclei.

Cushing[24] reported clinically three perforated ulcers following craniotomy with a fatal outcome in each instance.

It has not been possible, however, to reproduce typical gastric and duodenal lesions consistently by any of these methods and other avenues of approach appear more profitable.

D. Bacterial Methods.—Turck[103] (1906) produced ulcers in dogs by feeding *Bacillus coli communis.* However, Bauer[3] (1910) was unable to confirm Turck's findings and stated that the alleged ulcers were only pseudo-ulcers which were similar to Peyer's patches. From the published photographs in Turck's paper, it would appear that Bauer was correct.

Rosenow[95] has published several papers dealing with this subject and has reported the production of gastric and duodenal ulcers which resemble those in man by the intravenous injection of alleged specific streptococci. However, Wilensky and Geist[119] were unable to confirm Rosenow's work.

They made defects in the stomach wall of cats and implanted cultures of organisms from a human ulcer with negative results.

Ivy[52] injected cultures of streptococci into two or three branches of the gastroepiploic arteries in a series of dogs, with negative results.

Bacteria were also fed by mouth, and lacerations which had been made in the gastric mucosa healed in normal time and no ulcers developed. However, in cachectic animals, chronic ulcer was occasionally observed.

Hoffmann[50] (1925) was able to produce ulcer in guinea pigs by injecting, intra-abdominally, a solution of stomach contents from patients with ulcer. He was also able to reproduce the findings in other guinea pigs by injecting cultures taken from the induced ulcers.

It is well known that ulcer is a disease which occurs in individuals who are otherwise healthy and, in the light of our other knowledge, it seems unlikely that bacteria play a very significant role in the genesis of ulcer.

E. Methods Involving Dietary Alterations.—Kim and Ivy[60] fed neutral gastric mucin to seventeen dogs with external biliary fistula and prevented the development of ulcer.

Smith and McConkey[101] noted ulcers in 26 per cent of guinea pigs placed on a diet deficient in vitamin C. Diets deficient in vitamins A, B, or D did not cause ulcer if the vitamin C intake was adequate.

Weech and Paige[117] found ulcers in eight (36 per cent) of twenty-two dogs placed on a protein deficient diet. An additional 23 per cent showed erosions without true ulcer formation.

Wu[123] observed that subcutaneous injections of histidine would not protect animals against the development of ulcer after the Mann-Williamson operation. These observations were contrary to those of Weiss and Aron.[118]

Cheney[23] produced ulcers in chicks by deficient diets and observed hyperacidity in the chicks with ulcer.

Again, it is appreciated that ulcer occurs quite universally in people who have subsisted on a variety of diets and thus here, too, it seems unlikely that dietary alterations would play more than a minor role in the production of ulcer.

F. Methods Employing Certain Drugs.—These methods usually include the injection of a drug into an intact animal or directly into the wall of the stomach. A wide variety of drugs has been used and it is possible to produce acute ulcer with a number of different substances. Underhill and Freiheit[105] (1928) found that acute ulcerations could be produced in a rabbit's stomach with toxic doses of pilocarpine. They noted similar findings using a combination of pilocarpine and epinephrine but epinephrine alone would not produce the lesions. The ulcerations appeared more pronounced with an acid condition in the stomach and the pilocarpine caused a marked increase in peristalsis.

Light, Bishop, and Kendall[65] were able to produce gastric ulcers in rabbits in 94 per cent of instances by injecting only 10 mg. of pilocarpine into the lateral cerebral ventricles. A similar proportion was noted with subcutaneous administration only if the dose was increased to at least 75 mg.

Van Wagoner and Churchill[106] (1932) first noted gastric and duodenal ulcers in experimental cinchophen poisoning. Stalker, Bollman, and Mann[102] continued the inquiry and noted that the gastric acidity was, apparently, unchanged but there was an increased secretion when the ulcer was developing. They believed the lesion started as diffuse

gastritis which developed into superficial erosions and acute ulcers which occasionally became chronic. They were able to produce the lesion in dogs by administering the drug either orally, intravenously, subcutaneously, rectally, or by injection into an intestinal fistula. Simonds[100] believed that cinchophen ulcers originated in areas of purulent gastritis and that hyperacidity was not a significant factor.

Dodds and co-workers[28] produced a lesion in the fundus of a rabbit's stomach by the injection of posterior pituitary extract. The lesion was markedly limited to the acid-bearing area, however, and was not at all similar to clinical ulcer.

Metz[81] has reproduced the findings in the rabbit's stomach, but also states the lesion is in no way similar to peptic ulcer occurring in man and has, on the contrary, treated clinical ulcers using pituitary extract with encouraging results.[82]

Hanke[43] noted ulcer in cats after daily injections of 2 to 3 Gm. of caffeine sodium salicylate. Kanatake[57] produced ulcer by subcutaneous administration of various aliphatic amines.

The highest incidence of positive results, however, has followed the use of histamine. The profound effect of histamine upon gastric secretion has long been appreciated.

McIlroy[70] (1928) made traumatic lesions in the prepyloric region of cats. He then injected histamine in 10 to 20 mg. doses on alternate days and noted extension of the original lesion in all except one instance. He attributed the results to the increased hydrochloric acid induced by the histamine.

Büchner and Molloy[14] (1927) produced ulcer in about 33 per cent of rats, employing doses of 6 to 12 mg. histamine per 100 Gm. of body weight. Atropine in 0.5 mg. doses did not change the effect.

Büchner, Siebert, and Molloy[15] (1928) continued the study and noted an increased incidence of ulcer by starving the animals on alternate days.

Bürkle-de la Camp[16] (1929) enlarged upon Büchner's work. He also produced ulcer in rats by histamine injection and starvation, and observed that the results were not altered by dividing both vagi. He was, however, unable to produce ulcer in an intact dog, even combined with two to three days' starvation, but demonstrated delayed healing in artificially produced ulcers.

Matseuda[77] (1931) produced ulcers and erosions in 60 per cent of guinea pigs, 33 per cent of dogs, and 22 per cent of rabbits using doses of histamine ranging from 1 to 3 mg. per kilogram given three times daily.

O'Shaughnessy[89] (1931) noted ulcer in two of five cats by injection of a histamine solution into the muscular layer of the stomach wall. One ulcer was quite similar to a chronic ulcer in man.

Harde[44] (1932) was able to produce subacute and chronic lesions in the stomach of mice by subcutaneous injections of 0.25 mg. histamine. He noted no lesions in rabbits and only a few in guinea pigs with a dose of 1 mg. per animal.

Eppinger and Leuchtenberger[34] (1932) observed edema, swelling, and reddening in the gastric mucosa of the dog, following histamine injections. There were punctate and hemorrhagic erosions but no true ulcers.

Friedenwald, Feldman, and Morrison[39] (1933) assayed the effect of a number of substances by direct injection into the gastric wall. They employed representatives of fats, CHO, protein, metals, and other chemicals, principally various strengths of hydrochloric acid. They were able to produce only one small healed ulcer, employing histamine. Acute ulcer could be produced quite regularly by injecting 1 per cent hydrochloric acid into the stomach, and when histamine was given concurrently by subcutaneous administration, no evidences of chronicity followed. They, therefore, concluded that the prolonged administration of histamine is not a factor in the production of chronic ulcer.

Carnot and co-workers[17, 18] (1933), on the contrary, observed quite the opposite effects. They produced ulcer by injecting varying amounts and concentrations of hydrochloric acid directly into the stomach wall. They then attempted to observe any effect of the addition of 1 mg. histamine.

They found that the ulcers were not located exclusively along the lesser curvature and were more numerous. The lesions presented a hemorrhagic appearance and some ulcers appeared more chronic with less tendency to heal.

Flood and Howes[38] (1934) observed that the subcutaneous administration of histamine interfered with the healing of a mucosal defect in the prepyloric region of the stomach of the cat and dog, but had little effect if the defect were made high on the greater curvature.

Orndorff, Bergh, and Ivy[88] (1935) made a very diligent effort to produce ulcer with histamine. They injected dogs with 2 mg. of aqueous histamine every two hours, ten times a day. During the remaining four hours, the animals were fed. They produced erosions in the duodenum of four of nine dogs but no true ulcers. Using pilocarpine in 2.5 mg. doses, they observed extensive mucosal hemorrhages throughout the stomach and intestine in six of thirteen dogs. Employing a combination of histamine and pilocarpine, they observed mucosal hemorrhages and erosions in thirteen of twenty-five dogs, but no instance of a definite ulcer.

Heinlein and Kastrup[48] (1938), using cats, noted a gastritis with edema and mucosal hemorrhages following large intravenous doses of histamine but failed to observe either erosions or ulcers. They noted an elevation of the acid values, but believed they played only a secondary role in the genesis of ulcer.

Code and Varco[19] (1940) first noted the profound sustained effect upon gastric secretion following the injection of a histamine-beeswax mixture. Copious quantities of highly acid juice were secreted and the effect lasted at least twenty-four hours in the majority of cases.

Walpole and co-workers[110] had been able to produce erosions and ulcerations in cats quite readily by the daily instillation of 0.4 per cent hydrochloric acid. They, therefore, attempted a comparison between ulcer production in response to endogenous and exogenous acid. Seven cats were injected with daily doses of 20 mg. of histamine, and ulcers were noted in all instances.

Varco[108] utilized the same technique but used the dogs with significant results. Typical gastric and duodenal ulcer occurred in every instance. It thus became apparent that the duodenal ulcers were due

to the continuous excessive secretion of a highly acid gastric juice, evoked by the histamine-beeswax mixture.

Hay and associates[47] (1942) extended the study to include nearly all the common laboratory animals as well as the pig, chicken, calf, and woodchuck.

Typical gastric and duodenal ulcers were again observed in a high percentage of animals studied, indicating the applicability and merit of the method. By substituting caffeine rather than histamine in the beeswax mixture, Judd[55] was able to produce ulcerations in cats and guinea pigs and, similarly, using morphine. Merendino[80] produced ulcer also in cats and guinea pigs.

Thus, for the first time, a method became available for producing typical chronic gastric and duodenal ulcers in a variety of intact laboratory animals. The importance of highly acid gastric juice in the genesis of ulcer was definitely established.

G. Miscellaneous Methods.—Bolton[13] (1910) produced acute gastric ulcer in the cat by utilizing a "gastrotoxin" prepared by immunizing a goat with a cat's gastric cells. He then injected the goat's serum into the stomach wall of the cat, producing an acute ulcer.

Mann[72] (1916) noted acute ulcers in a large percentage of dogs and cats dying after bilateral adrenalectomy where symptoms of adrenal insufficiency had developed.

Ivy[52] noted four acute ulcers and numerous petechial hemorrhages in twenty-four thyroid-parathyroidectomized dogs.

Shapiro and Ivy[99] (1926) produced acute ulcers with local allergic phenomena by sensitizing an animal to a specific protein.

Wolfer[120] (1926) exposed the lumen of the stomach and gave x-ray radiation for thirty minutes with subsequent development of ulcer.

Kabat and Hedin[56] noted erosions and ulcerations in cats, following severe burns, and Merendino[80] has produced ulcer by fracturing the long bones of experimental animals, both methods probably being related to the release of histamine or a histamine-like substance.

Thus, in summary, after a fairly complete survey of the literature, it would appear that Code's method of the implantation of a histamine-beeswax mixture provides the best means of producing typical chronic duodenal and gastric ulcer. It is freely admitted that ulcer may be produced by a variety of methods, but the majority of them invoke alteration of the normal anatomy and physiology of the animal.

The value of producing typical lesions at will, in an intact animal, is obvious and Code's methods fulfill that criterion admirably.

DESCRIPTION OF THE METHOD, OPERATIVE PROCEDURES AND RESULTS

For nearly fifty years, surgeons have been treating ulcer quite empirically, employing a variety of operations without any definite knowledge of what their operation would accomplish. Their only criterion of success was the prevention of recurrence of the ulcer. It is indeed unfortunate that the initial improvement which follows almost any operative procedure upon the stomach was not better understood. Nearly any operation which increases the emptying time of the stomach and deviates the acid gastric juice away from the ulcerated duo-

denum will allow healing of the duodenal ulcer, only to be followed at some future date by the even more distressing jejunal ulcer.

Thus, surgeons, encouraged by their early successes and without appreciating the unfortunate results to come, performed operations in increasing numbers and eventually found many of their patients in a far worse predicament than if no operation had been done. One cannot help but wonder how many lives have been lost by inflicting upon patients such disastrous operations as those suggested by Von Eiselsberg,[109] Schmilinsky,[97] and Devine[27] when these people might have struggled along for years, suffering intermittently with their ulcers but still alive. It is not surprising that internists became hesitant to suggest operation to their patients when no definite improvement could be assured.

All this has changed. The importance of the acid factor has been demonstrated repeatedly and convincingly. Thus, the most important criterion which a satisfactory operation for ulcer must fulfill is effectual reduction of gastric acidity. Operations which fail to accomplish this leave too much to chance and will certainly be followed by a definite percentage of failure. With the means available for producing ulcer consistently in a number of laboratory animals, the protective influence of a variety of operative procedures may be assayed. The patient need no longer be made to serve as an experimental animal for new and untried procedures.

The value of twelve operative procedures has been subjected to experimental scrutiny and an attempt made to correlate the findings with the clinical data already available.

These operations include the majority of the commonly employed procedures in the surgical treatment of ulcer with the possible exception of pyloroplasty which was omitted because of its close relationship to gastrojejunostomy.

It is admitted that surgery is not the final answer to the ulcer problem. Surgical intervention is necessary only because medical management fails and the surgeon would be the first to relinquish his part if other equally as satisfactory conservative means were at hand. It is somewhat of an admission of defeat to remove an extensive segment of the stomach to heal a small stubborn duodenal ulcer and might be likened to the sacrifice of a lower limb in an attempt to control a diabetic gangrene involving only the toes and foot.

However, until better means are available, it would appear that surgery offers the best chance of effectively controlling gastric acidity.

The rarity of spontaneous ulcer in the dog has been recognized by a number of investigators;[52, 72, 104] therefore, dogs were chosen as the laboratory animals for these investigations.[63]

The dogs were fasted for twelve hours prior to operation. The operative procedures were done under intratracheal ether anesthesia. All anastomoses were accomplished by the closed aseptic technique as described by Wangensteen.[111] The animals were supported during the immediate postoperative period by daily intravenous infusion of glucose and saline solutions.

A period of three months was then allowed to elapse before the histamine injections were initiated to insure complete recovery from

the operative procedures. During this period, the animals were fed the usual stock diet consisting of commercial dog biscuit, supplemented occasionally by raw meat and table scraps.

The injection periods were then instituted. These were done daily, at about 5 P.M., following which the feed pans were removed and no food was allowed until the next morning. The technique of preparing the histamine-in-beeswax mixture has been described in detail elsewhere[20, 47] and the daily dose of 30 mg. of histamine base was employed in all instances. The injections were made intramuscularly in multiple sites along the spinal muscles to insure adequate liberation of the histamine.

The symptoms of a developing ulcer were usually easily recognized. The animals became listless, cachectic, refused food, and, frequently, blood vomitus or tarry stools could be observed. Obviously moribund animals were sacrificed in order to obtain fresh autopsy specimens. The surviving animals were sacrificed at the end of the forty-day injection period. In each series of animals control dogs were injected and all of them developed typical duodenal ulcer. Grossly, these ulcers are quite similar in appearance to those developing spontaneously in man, with hemorrhage, excavation, induration, and perforation being commonly observed.

Microscopic sections of the ulcer were made in each instance and the findings were quite uniform. The free perforations obviously showed a loss of all the layers of the bowel wall and the chronic ulcers demonstrated a loss of the mucosal and submucosal layers with heaped-up overhanging edges and a leucocytic infiltration at the base of the ulcer. No tendency toward healing was noted.

I. Group I—Gastrojejunostomy

Gastrojejunostomy is perhaps the oldest of the operative procedures employed in the treatment of ulcer. Although Wölfler's initial procedure (1881) was for inoperable carcinoma, the operation of von Hacker (1885) was quite similar to the one usually done today.

About the turn of the century, reports of jejunal ulcer following gastrojejunostomy began to appear in the literature. Thus, surgeons began to seek out other more satisfactory procedures. The European surgeons were far in advance of the American surgeons in employing the more radical gastric resection in the treatment of ulcer.

Gastrojejunostomy continued to enjoy widespread popularity in this country with the exception of a few surgeons as A. A. Berg, Lewisohn, and Strauss, who pioneered the more radical gastric resection.

The formidable mortality which accompanied gastric resection in its early years makes it easily understandable why the less hazardous gastrojejunostomy was more acceptable.

However, with the present-day mortality rate of resection comparing favorably with that of gastrojejunostomy and the numerous unfavorable reports of jejunal ulcer following the conservative procedures, the once widespread popularity of gastrojejunostomy is gradually waning. The incidence of recurrent ulcer, following gastrojejunostomy, has been reported in wide variation, ranging between 2 and 30 to 40

per cent, and is probably due to difference in indications and age groups. Instances of recurrent ulcer, developing from twenty to thirty years following the initial gastrojejunostomy, are not unusual although the average interval is probably about five years.

Thus, a true estimate of the ultimate occurrence must certainly approach 15 per cent.

The alleged benefits of gastrojejunostomy are due not only to the new avenue of escape for the stomach contents but also to the regurgitation of the alkaline duodenal juices into the stomach with neutralization of the gastric secretion.

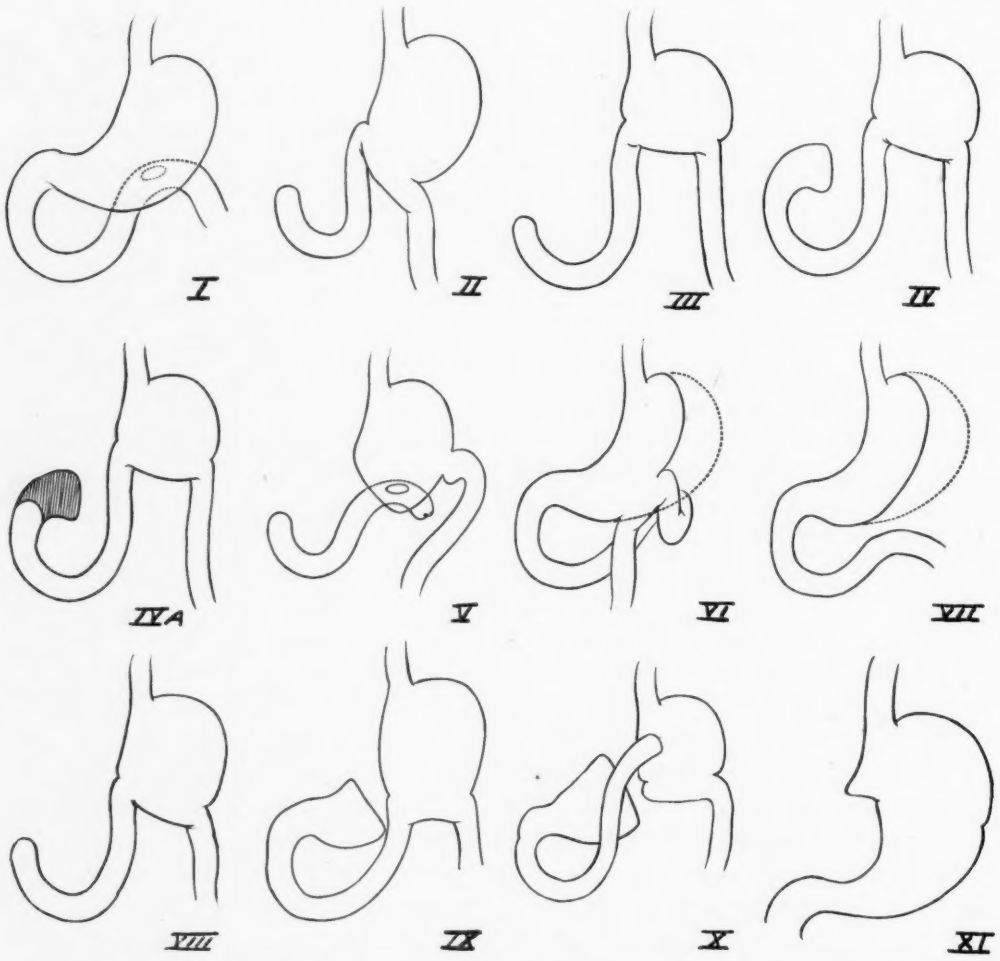


Fig. 1.—*I*, Gastrojejunostomy; *II*, small gastric resection or antral excision; *III*, extensive three-quarter gastric resection; *IV*, Finsterer antral exclusion; *IVA*, Finsterer antral exclusion with excision of antral mucosa; *V*, antral resection plus total intragastric regurgitation, Schmilinsky procedure; *VI*, fundusectomy with gastrojejunostomy; *VII*, fundusectomy; *VIII*, hemigastrectomy; *IX*, Devine exclusion; *X*, modified Devine exclusion with total intragastric regurgitation; *XI*, sleeve resection of segmental gastrectomy.

Although the gastric acidity is usually lowered following this procedure, in the experience of this clinic, none of the patients with duodenal ulcer studied was persistently achlorhydric and the incidence of jejunal ulcer was 10 per cent.[114, 115] Therefore, the procedure has been almost entirely abandoned in this clinic, and only seven deliberate gastrojejunostomies for ulcer have been performed in the past five years.

TABLE I

INCIDENCE OF JEJUNAL ULCER FOLLOWING GASTROJEJUNOSTOMY

DOG NUMBER	WEIGHT (LB.)	NUMBER OF INJECTIONS	RESULTS	REMARKS
1	34	3	Perforated* 2.5 cm. jejunal ulcer	Dog expired, peritonitis
2	29	40	2 cm. jejunal ulcer	Also numerous erosions in jejunum
3	36	13	Perforated 1.5 cm. jejunal ulcer	Dog expired, peritonitis
4	30	40	2 cm. jejunal ulcer	

*See Fig. 2.

Gastrojejunostomy was performed on four dogs. It will be noted (Table I) that ulcer developed in all the animals, and two dogs expired from peritonitis, due to large, perforated jejunal ulcers.

It thus becomes apparent that this operation offers no protection against the development of ulcer but, on the contrary, appears to expedite its occurrence. All the ulcers developed in the jejunum, and no duodenal or gastric ulcers were observed.

It must be admitted that this operation occasionally is of value, especially in the older patients whose principal difficulty is obstruction, but with the operative risk of gastric resection approaching that of the more conservative gastrojejunostomy, these instances must be quite infrequent.

II. Group II—Small Gastric Resection or Antral Excision

It is the small gastric resection or antral excision which is partly responsible for the statement that gastric resection offers no more protection against the occurrence of recurrent ulcer than does gastrojejunostomy.

It is not unnatural that surgeons undergoing the transition between the conservative and the more radical procedures were somewhat timid in the extent of their resection. Thus, the first partial gastrectomies were hardly more than pylorectomies or antrectomies.

However, recurrent ulcers were also observed following this operation and thus gastric resection fell into disrepute.

The operation fails to reduce adequately gastric acidity and must be considered unsatisfactory. In a small series of cases observed in this clinic, none of the patients was persistently achlorhydric following this procedure and the incidence of jejunal ulcer was 33 per cent.[114]

TABLE II

INCIDENCE OF JEJUNAL ULCER FOLLOWING SMALL GASTRIC RESECTION

DOG NUMBER	WEIGHT (LB.)	NUMBER OF INJECTIONS	RESULTS	REMARKS
185	35	40	2 cm. jejunal ulcer	
187	32	40	2 cm. jejunal ulcer	Ulcer almost perforated, also marked jejunitis
196	35	35	2 cm. jejunal ulcer*	Dog moribund, entire intestinal tract filled with old blood
26	15	40	1 cm. jejunal ulcer	

*See Fig. 3.

The operation consists of resection of the antral segment of the stomach which comprises only 25 to 30 per cent of the total area. Continuity is then established by gastrojejunostomy, following the Billroth II pattern. This procedure was performed on four dogs.

Ulcer again developed in all animals (Table II), although three of the four survived the injection period. The other dog became moribund after a large hemorrhage and was sacrificed following thirty-five injections.

Fig. 2.

Fig. 3.

Fig. 2.—Perforated jejunal ulcer (Dog 1) following gastrojejunostomy. Dog expired from peritonitis after three injections of the histamine-in-beeswax mixture.

Fig. 3.—Large jejunal ulcer (Dog 196) following small gastric resection. Dog sacrificed after thirty-five injections of histamine-in-beeswax mixture, moribund from hemorrhage.

This operation presents the opportunity of testing the validity of the Edkins' hypothesis.[32] It will be remembered that he postulated the presence of an antral hormone, "gastrin," which regulated the acid secretion of the fundus. Thus, by removing this hormonal mechanism, the acidity of the gastric secretion should be reduced so that ulcer would not occur.

This procedure, then, would tend to invalidate this thesis, as although the entire antral segment is removed, ulcer still develops. It is thus apparent that this operation is entirely inadequate and the sacrifice of a larger segment of the stomach is necessary to reduce effectively gastric acidity and to protect against recurrent ulceration.

III. Extensive Gastric Resection

Although the partial gastrectomy or antrectomy has been quite generally discontinued, the more extensive resections are still subject to

some variation in different clinics. The surgeon must be able to show good reason for sacrificing an extensive segment of stomach.

The ideal resection should remove a portion of the stomach which will effectively control gastric acidity and insure protection against recurrent ulcer and yet leave the patient with a residual pouch large enough to provide a satisfactory gastric capacity. The three-quarter resection would appear to satisfy this requirement.

This operative procedure includes resection of the distal 75 per cent of the stomach, followed by anastomosis with the first portion of the jejunum and inversion of the lesser curvature, according to the Hofmeister pattern. This operation was done on four dogs.

TABLE III

INCIDENCE OF JEJUNAL ULCER FOLLOWING EXTENSIVE GASTRIC RESECTION

DOG NUMBER	WEIGHT (LB.)	NUMBER OF INJECTIONS	RESULTS	REMARKS
6	38	40	No ulcer	
23	20	40	No ulcer	
24	47	40	No ulcer*	Few small submucosal hemorrhages in gastric pouch
28	27	40	No ulcer	Mild gastritis with 1 small erosion adjacent to esophagus

*See Fig. 4.

Thus, this operation completely protects the dog against the development of an experimentally induced ulcer. The resection of an extensive segment of the stomach alone, however, is not enough, as additional factors must be considered.

The importance of the length of the proximal afferent loop cannot be overemphasized. The increasing susceptibility to acid gastric juice of the lower intestinal tract has been attributed to decreased tissue resistance by Harper,[45, 46] McMaster,[71] Matthews and Dragstedt,[79] and others. Although there is good evidence to support this thesis, it seems possible that another factor may play a role. It has been shown that the duodenum and the upper jejunum are the most potent sources of "secretin," the hormone which regulates the secretion of the alkaline pancreatic juice.[4] It is also known that the acid gastric secretion is necessary to activate the secretin and this stimulates the secretion of pancreatic juice. Thus, if the acid gastric secretion were introduced into the jejunum, below the secretin-containing segment of duodenum and upper jejunum, the secretion of pancreatic juice might be inadequate to neutralize the acid gastric juice, and jejunal ulcer would result. Studies are now being made to determine which of the two factors, tissue susceptibility or the secretin response, is the more important. However, no matter which mechanism is the more responsible, sufficient experimental and clinical evidence is available to condemn the long afferent loop. Merendino[80] has performed extensive three-quarter gastric resection in the dog and, by employing a long 75 cm. afferent loop, has observed two perforated jejunal ulcers after employing the histamine-in-beeswax injections.

Kiefer,[59] reporting the experiences of the Lahey Clinic, admits an incidence of recurrent ulcer in 12 (6.9 per cent) of 173 patients upon

whom an extensive gastric resection had been performed for duodenal ulcer. An additional 8 patients (4.6 per cent) exhibited postoperative hemorrhage although no definite ulcer was demonstrated. Thus, the results obtained in 20 (11.5 per cent) patients were clearly unsatisfactory. The gastric resection was apparently quite extensive but Lahey is an ardent advocate of the long loop anterior anastomosis.

In a recent review from this clinic, the results following 241 resections were studied.[62] Of that number, 140 operations were done for duodenal ulcer, 23 for duodenal and gastric ulcer occurring coincidentally, and 25 for gastrojejunal ulcer. The remainder of the operations were done for gastric and pyloric ulcers.

The operation done in every case was the three-quarter resection with the anastomosis being made posterior to, right at, or even proximal to, the ligament of Treitz. Not a single instance of recurrent jejunal ulcer has been observed following this procedure.

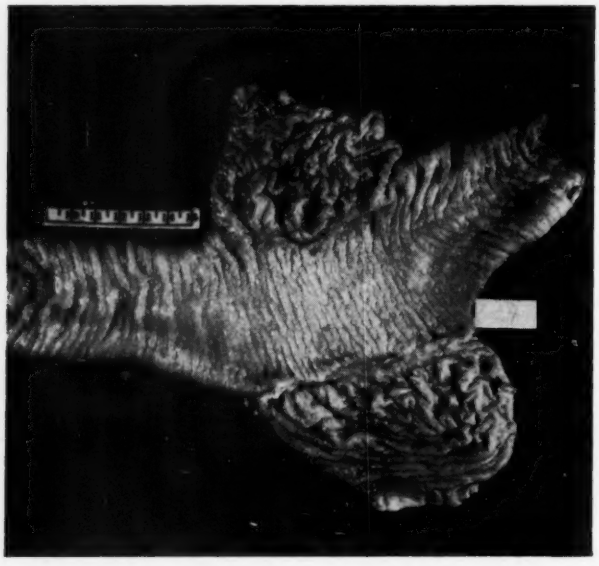


Fig. 4.—Normal jejunum (Dog 24) after extensive gastric resection. Note the short afferent loop. Dog sacrificed after forty injections of histamine-in-beeswax mixture.

Thus, experimental and clinical evidence clearly favors the short afferent loop. It is unfortunate that technical difficulties render impossible the employment of the Billroth I pattern of anastomosis as it would certainly be the most physiologic procedure.

The extensive three-quarter resection with the short loop anastomosis would thus appear to be most satisfactory, both from an experimental and clinical background.

It might indeed be argued that a slightly less extensive resection would prove equally as satisfactory, especially in the cases in the older age group or in the patients with gastric ulcer.

However, the results following approximately 300 resections, which have been done to date for gastric and duodenal ulcer, have been so consistently gratifying, that it would not seem necessary to employ a less certain procedure.

IVA. Finsterer Antral Exclusion With Excision of Antral Mucosa

This operative procedure is identical with the Group III operation except for the technical variation of inversion of the duodenum. The difficulties in dealing with the so-called "inoperable" duodenal ulcer are familiar to all gastric surgeons. They are also aware of the unhappy results obtained when attempting to deal with such a problem by employing one of the exclusion procedures of Von Eiselsberg,[109] Finsterer,[37] or Devine.[27]

Although actual excision of the ulcer is unimportant, the necessity of ablating the antral mucosa is now quite apparent. A number of surgeons, notably, Plenk,[93] Bancroft,[2] Wolfson and Rothenberg,[121] and Wangensteen[112, 113] have concerned themselves with this problem. The "gastrin" thesis of Edkins has previously been mentioned.

Thus, the antral mucosa is excised and the closure accomplished by employing the antral musculature. This procedure was done on four dogs (see Table IVA).

TABLE IVA

INCIDENCE OF JEJUNAL ULCER FOLLOWING FINSTERER ANTRAL EXCLUSION WITH EXCISION OF ANTRAL MUCOSA

DOG NUMBER	WEIGHT (LB.)	NUMBER OF INJECTIONS	RESULTS	REMARKS
46	26	40	No ulcer	Several erosions in gastric pouch, especially about esophagus; antral musculature markedly shrunken
48	35	40	No ulcer	Findings similar to Dog 13
64	48	40	No ulcer	
82	36	40	No ulcer	

The results (Table IVA) in this group are thus equally as acceptable as those in the previous series.

Although this procedure is of little experimental value, it has proved to be an invaluable adjunct in dealing with what might be an exceedingly difficult situation. This procedure has now been done in approximately forty patients with equally as satisfactory results as following the Group III operation.

IV. Finsterer Antral Exclusion

This procedure is again identical with the Group III operation except for the antrum which is not removed. The stomach is divided about 5 to 6 cm. proximal to the pylorus and the distal end is inverted. The operation was done on four dogs.

In attempting to correlate the findings in this group (Table IV) with the Edkins' hypothesis, it would appear that the results are suggestive but not conclusive. The erosions in the gastric pouch were more numerous than in either of the two preceding groups but the findings in the jejunum were essentially unchanged.

Fauley, Strauss, and Ivy[36] did Finsterer type resections in twelve dogs and observed the development of three (25 per cent) jejunal ulcers within seven months. They excised about 66 per cent of the stomach, including the antrum, and made the anastomosis with the first loop of jejunum.

TABLE IV

INCIDENCE OF JEJUNAL ULCER FOLLOWING FINSTERER ANTRAL EXCLUSION

DOG NUMBER	WEIGHT (LB.)	NUMBER OF INJECTIONS	RESULTS	REMARKS
12	43	32	Several erosions in jejunum with marked jejunitis	Dog expired after 3 injections
29	41	40	No ulcer	Numerous erosions throughout gastric pouch with antral gastritis
30	37	40	No ulcer	Numerous erosions in gastric pouch
36	37	40	No ulcer	As in Dog 19

In this clinic, the incidence of jejunal ulcer following this type of operation is 8.5 per cent and other surgeons have reported even more unsatisfactory results. One patient, in particular, illustrates the significance of the antrum quite convincingly. Following a Finsterer exclusion operation, he continued to have difficulty and exhibited high acid values repeatedly. At a secondary operation, the residual antral segment, which measured only 16 sq. cm., was excised, following which the patient became almost completely achlorhydric with a complete cessation of symptoms.

Thus, although conclusive experimental data are lacking, accumulated evidence would suggest that this procedure should be discarded in favor of the Group III or IVA operation.

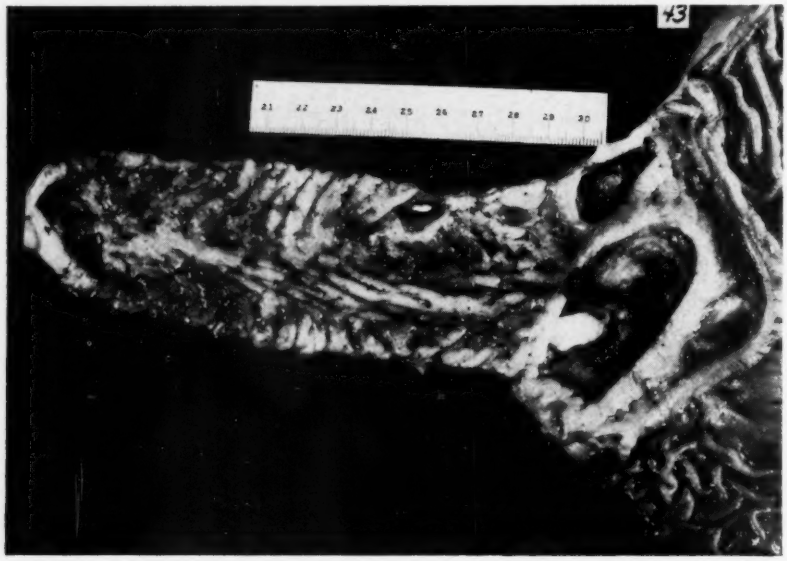


Fig. 5.—Multiple jejunal ulcers (Dog 43) following Schmilinsky procedure. Dog expired from hemorrhage and peritonitis after eleven injections of histamine-in-beeswax mixture.

V. Antral Resection Plus Total Intragastric Regurgitation

This procedure as advocated by Schmilinsky[97] was performed on four dogs.

The entrance of all the alkaline bile and pancreatic juice into the stomach would at first sight appear to be a desirable feature. However, it soon became apparent that it was quite the contrary.

TABLE V

INCIDENCE OF JEJUNAL ULCER FOLLOWING ANTRAL RESECTION PLUS TOTAL INTRAGASTRIC REGURGITATION

DOG NUMBER	WEIGHT (LB.)	NUMBER OF INJECTIONS	RESULTS	REMARKS
38	27	40	1.5 cm. jejunal ulcer	
41	27	2	Perforated 1 cm. jejunal ulcer	Dog died, peritonitis
43	40	11	4 jejunal ulcers,* 2 perforated	Dog died, peritonitis; also old blood in intestine
49	47	8	Perforated 1 cm. jejunal ulcer	Dog died, peritonitis

*See Fig. 5.

The explanation of such a formidable incidence of jejunal ulcer is not altogether clear, although it might be due to an interminable stimulation of the second (gastric) phase of gastric secretion by the bile and pancreatic juice or a failure of liberation of secretin.

Whatever the explanation, it is obvious that this procedure enhances, rather than protects against, the development of jejunal ulcer and is thus to be condemned. Fortunately, it was only performed on three patients, two (66 per cent) of whom promptly developed jejunal ulcer.[114]

VI. Fundusectomy With Gastrojejunostomy

This procedure was first suggested by Connell in 1929.[22] He maintained that excision of the fundic portion of the stomach would effectively reduce gastric acidity and recommended the operation for its simplicity because no anastomosis was necessary.

However, Seely and Zollinger[98] and Watson[116] have shown that although acid values may be initially reduced, within a few months they will return to preoperative levels.

In this group, fundusectomy was combined with gastrojejunostomy and was done on four dogs.

TABLE VI

INCIDENCE OF ULCER FOLLOWING FUNDUSECTOMY WITH GASTROJEJUNOSTOMY

DOG NUMBER	WEIGHT (LB.)	NUMBER OF INJECTIONS	RESULTS	REMARKS
31	42	40	No ulcer	Mild jejunitis
33	35	40	No ulcer	Few erosions in gastric pouch
54	40	40	No ulcer	
78	30	40	No ulcer	

Thus, this procedure appears to furnish satisfactory protection against the development of jejunal ulcer (Table VI) although, clinically, the gastric capacity following this operation is less adequate than that following the Group III or IVA procedure as the most dilatable portion of the stomach is removed. No jejunal ulcer has been observed clinically in eight patients upon whom this operation has been done, although only two (25 per cent) are persistently achlorhydric.

VII. Fundusectomy

The operation in this series approximates Connell's original description and was done on four dogs.

TABLE VII

INCIDENCE OF ULCER FOLLOWING FUNDUSECTOMY

DOG NUMBER	WEIGHT (LB.)	NUMBER OF INJECTIONS	RESULTS	REMARKS
19	32	40	No ulcer	Mild antral gastritis
21	25	40	Small duodenal erosions	Marked antral gastritis
22	37	40	Duodenal erosion	Antral gastritis
75	27	40	Duodenal* ulceration	Submucosal antral hemorrhages

*See Fig. 6.

This procedure, therefore, offers less protection than the preceding one (Table VII). Both again offer opportunity to evaluate Edkins' hypothesis. It would appear, especially from the results in Group VII, that the evidence favored the Edkins' thesis as although the extent of the resection in this group (VII) is as great as in the Group III or IVA operation, the findings following fundusectomy, in which the antrum remains in situ, are considerably different.

Fig. 6.—Duodenal ulcer (Dog 75) following fundusectomy. Dog sacrificed after forty injections of histamine-in-beeswax mixture.

None of the five patients upon whom this operation was done became achlorhydric and symptoms from the ulcer continue in two of them, one of whom subsequently had the antrum and pylorus excised.

Thus, the principle of fundusectomy cannot compete favorably with the Group III or IVA procedures, and the clinical indications for such an operation would also be much more limited.

VIII. Hemigastrectomy

Hunt[51] has questioned the necessity of the extensive three-quarter gastric resection and advocated a more conservative procedure or hemigastrectomy. Accordingly, this operation was done on four dogs.

It would thus appear (Table VIII) that the operation does not furnish adequate protection. Hunt admits the possibility of an occasional jejunal ulcer but considers that less important than the impairment of gastric function which he alleges follows the more extensive resection.

TABLE VIII

INCIDENCE OF JEJUNAL ULCER FOLLOWING HEMIGASTRECTOMY

DOG NUMBER	WEIGHT (LB.)	NUMBER OF INJECTIONS	RESULTS	REMARKS
58	36	4	4 jejunal* ulcers, 1 perforated	Dog died, peritonitis
62	31	40	No ulcer	Marked gastritis
73	18	40	No ulcer	
77	26	40	Jejunal erosion, no ulcer	

*See Fig. 7.

The experience of this clinic, however, would suggest that the weight of evidence tips the scales in the opposite direction. The unsatisfactory results and the necessity of even an occasional reoperation would appear to be far more disturbing than the incidence of any degree of impairment of gastric function observed in this clinic.

Fig. 7.

Fig. 8.

Fig. 7.—Multiple jejunal ulcers (Dog 58) following hemigastrectomy. Dog expired from peritonitis after four injections of histamine-in-beeswax mixture.

Fig. 8.—Large jejunal ulcer following Devine exclusion. Dog sacrificed after forty injections of histamine-in-beeswax mixture.

Hemigastrectomy would undoubtedly prove to be eminently satisfactory in a great majority of instances, but in the light of the gratifying results accompanying the Group III and IVA operations, it would not appear advisable to accept even a small incidence of recurrent ulcer.

IX. Devine Exclusion

No additional experimental evidence is necessary to bring to light the dismal record of this operation. The experience of surgeons with this unfortunate procedure has been uniformly disastrous.

TABLE IX

INCIDENCE OF JEJUNAL ULCER FOLLOWING DEVINE EXCLUSION

DOG NUMBER	WEIGHT (LB.)	NUMBER OF INJECTIONS	RESULTS	REMARKS
88	38	34	Multiple jejunal ulcers; one 2 cm. ulcer	Dog died; peritonitis
89	42	40	Large 3 by 5 cm.* indurated jejunal ulcer	

*See Fig. 8.

It was added merely to complete the series and further test the efficiency of the method. The stomach was divided at about its lower third, the distal end inverted, and the jejunum anastomosed to the proximal gastric segment. This procedure was done on two dogs.

No further comment is necessary to condemn this procedure (Table IX).

X. Modified Devine Exclusion With Total Intragastric Regurgitation

The effects of total intragastric regurgitation have been mentioned and the failure of liberation of secretin suggested as a possible explanation. Thus the stomach was divided at about its mid-portion to assure the entrance of a definite quantity of acid gastric juice into the proximal loop. This loop was then implanted high on the fundus and the jejunum anastomosed to the proximal gastric segment. This procedure was done on two dogs.

TABLE X

INCIDENCE OF JEJUNAL ULCER FOLLOWING MODIFIED DEVINE EXCLUSION WITH TOTAL INTRAGASTRIC REGURGITATION

DOG NUMBER	WEIGHT (LB.)	NUMBER OF INJECTIONS	RESULTS	REMARKS
153	36	4	3 jejunal ulcers, 2 perforated	
154	30	28	2 jejunal ulcers 1 to 2 cm. in diameter	Dog sacrificed, moribund

Thus, this procedure is equally unsatisfactory (Table X). If any protective influence did arise from the activation of secretin, it would appear to have been overcome by the torrent of acid gastric juice. The principle of intragastric regurgitation would thus appear to be unsatisfactory.

XI. Sleeve Resection or Segmental Gastrectomy

The sleeve resection procedure has also been quite uniformly discarded by surgeons. The central 50 per cent of the stomach was resected, following which the antrum was anastomosed to the remaining proximal (25 per cent) gastric pouch. This procedure was done on two dogs.

Although the experimental evidence is not conclusive (Table XI), the clinical limitations of such an operative procedure are obvious.

Suspected malignancy in gastric ulcers, duodenal obstructions, or hemorrhage would preclude the employment of this operation.

TABLE XI

INCIDENCE OF ULCER FOLLOWING SLEEVE RESECTION OR SEGMENTAL GASTRECTOMY

DOG NUMBER	WEIGHT (LB.)	NUMBER OF INJECTIONS	RESULTS	REMARKS
142	36	40	No ulcer	Few submucosal antral hemorrhage
156	32	40	Small duodenal erosion	

Here again, the Edkins' hypothesis may be tested and, although not conclusive, the incidence would appear not to support this thesis as the extent of resection approximates that of the hemigastrectomy, but the results are certainly no worse and might even be better. It would appear, however, to support the Billroth I pattern of resection.

SUMMARY AND CONCLUSIONS

The preponderance of evidence suggests that the most important single factor in the causation of ulcer is an excess of unneutralized gastric acid. Accordingly, a satisfactory operation must control this item adequately. Code's histamine-in-beeswax preparation has made it possible to produce ulcer consistently in a variety of intact laboratory animals. It is also possible, therefore, to assay the protective ability of a number of operative procedures against the formation of ulcer. The experimental data obtained by employing this method would appear to substantiate the clinical data already available indicating the efficiency of this experimental approach to the ulcer problem. It also provides a means of evaluating any new or untried procedures without submitting the patient to an "experimental" operation.

A number of requirements which a satisfactory operation must fulfill have become apparent. First, an effective reduction of gastric secretion must be accomplished which necessitates the sacrifice of an extensive segment of gastric tissue, including the antrum and the lesser curvature.

Second, the manner of duodenal inversion, with or without removal of the ulcer, is of no great consequence, but all the antral mucosa must be removed.

Although experimental evidence favoring the Edkins' hypothesis is not conclusive, clinical experience has indicated clearly the importance of the antral mucosa.

Finally, the anastomosis with the jejunum must be made in such a manner that the proximal afferent loop is as short as possible. The possibilities of the secretin factor and decreased tissue susceptibility have been mentioned and the evidence condemning the long loop is conclusive.

1. Thus, gastrojejunostomy, hemigastrectomy, and the small gastric resection are inadequate operations, as they fail to reduce gastric secretion effectively.

2. The exclusion type of operation is unsatisfactory as the antral hormonal influence is uncontrolled.

3. The principle of total intragastric regurgitation is to be condemned.

4. The limited indications for the segmental resection or fundusectomy are mentioned.

5. The most satisfactory operation would appear to be an extensive three-quarter gastric resection, including the antrum, or at least the

antral, mucosa and making the anastomosis with the jejunum in such a manner that the proximal efferent loop is as short as possible.

This type of operation has now been done clinically with gratifying results in approximately 300 patients without a single instance of a recurrent jejunal ulcer.

REFERENCES

1. Bachrach, W. H., Schmidt, C. R., and Beazell, J. M.: The Relation of Bile and Pancreatic Juice to Duodenal Ulcer in Dogs, Proc. Soc. Exper. Biol. & Med. **40**: 322-324, 1939.
2. Bancroft, F. W.: A Modification of the Devine Operation of Pyloric Exclusion for Duodenal Ulcer, Am. J. Surg. **16**: 223-230, 1932.
3. Bauer, A.: Recherches experimentales sur la pathogenie de l'estomac, Arch. de mal. de l'appar. digest. **4**: 73-81, 1910.
4. Bayliss, W. M., and Starling, E. H.: Mechanism of Pancreatic Secretion, J. Physiol. **28**: 325, 1902.
5. Beaver, M. G., and Mann, F. C.: The Production of Peptic Ulcer After Section of the Gastric Nerve, Ann. Surg. **94**: 1116-1118, 1931.
6. Beazell, J. M., and Ivy, A. C.: Chronic Gastric Ulcer Following Bilateral Vagotomy in the Rabbit and in the Dog, Arch. Path. **22**: 213-219, 1936.
7. Berg, B. N.: Peptic Ulcers, Arch. Surg. **28**: 1057-1061, 1934.
8. Berg, B. N., and Jobling, J. W.: Biliary and Hepatic Factors in Peptic Ulcers, Arch. Surg. **20**: 997-1015, 1930.
9. Berg, B. N., and Zucker, T. F.: Comparative Frequency of Peptic Ulcers After Deprivation of Bile and Pancreatic Juice, Proc. Soc. Exper. Biol. & Med. **30**: 330-332, 1932.
10. Bickel, A.: Beobachtungen an Hunden mit extirpiertern duodenum, Berl. klin. Wchnschr. **46**: 1201-1202, 1909.
11. Blanck, E. E.: Peptic Ulcer; An Experimental Study, Surg., Gynec. & Obst. **61**: 480-493, 1935.
12. Bollman, J. L., and Mann, F. C.: Peptic Ulcer in Experimental Obstructive Jaundice, Arch. Surg. **24**: 126-135, 1932.
13. Bolton, C.: Further Observations on the Pathology of Gastric Ulcer, Proc. Roy. Soc., London **82**: 233-248, 1910.
14. Büchner, F., and Molloy, P. J.: Das echte peptische Geschwür der Ratte, Klin. Wchnschr. **6**: 2193-2194, 1927.
15. Büchner, F., Siebert, P., and Molloy, P. J.: Ueber experimentell erzougte akute peptische Geschwüre des Rattenvormagens, Beitr. z. path. Anat. u. z. allg. Path. **81**: 391-425, 1928.
16. Bürkle-de la Camp: Zur Pathologie und Chirurgie der peptischen Schädigungen des Magen-DarmKanals, Deutsche. Ztschr. f. Chir. **220**: 31-88, 1929.
17. Carnot, P., Simonnet, H., Tissier, M., and Cachera, R.: Contribution à l'etude des ulcères gastriques expérimentaux, Compt. rend. Soc. de biol. **113**: 1177-1181, 1933.
18. Carnot, P., Simonnet, H., Tissier, M., and Cachera, R.: Influence des injections répétées d'histamine sur l'évolution des ulcères gastriques expérimentaux, Compt. rend. Soc. de biol. **113**: 1517-1519, 1933.
19. Code, C. F., and Varco, R. L.: Chronic Histamine Action, Proc. Soc. Exper. Biol. & Med. **44**: 475-477, 1940.
20. Code, C. F., and Varco, R. L.: Prolonged Action of Histamine, Am. J. Physiol. **137**: 225-233, 1942.
21. Cohnheim, J.: Lectures on General Pathology, The New Sydenham Society **3**: 875, 1890.
22. Connell, F. G.: Fundusectomy: A New Principle in the Treatment of Gastric and Duodenal Ulcer, Surg., Gynec. & Obst. **49**: 696-701, 1929.
23. Cheney, G.: Gastric Acidity in Chicks With Experimental Gastric Ulcers, Am. J. Digest. Dis. **5**: 104-107, 1938.
24. Cushing, H.: Peptic Ulcers and the Interbrain, Surg., Gynec. & Obst. **55**: 1-34, 1932.
25. DeBakey, M. E.: Peptic Ulceration, Arch. Surg. **34**: 230-267, 1937.
26. De Takats, G., and Mann, F. C.: The Effect on the Jejunal Mucosa of Transplantation to the Lesser Curvature of the Stomach, Ann. Surg. **85**: 698-703, 1927.
27. Devine, H. B.: Basic Principles and Supreme Difficulties in Gastric Surgery, Surg., Gynec. & Obst. **40**: 1-16, 1925.
28. Dodds, E. G., Noble, R. L., Scarff, R. W., and Williams, P. G.: Pituitary Control of Alimentary Blood Flow and Secretion—Changes in the Stomach Produced by the Administration of Posterior Pituitary Extract, Proc. Roy. Soc., London **123**: 22-26, 1937.
29. Dott, N. M., and Lim, R. K.: Experimental Jejunal Ulcer, Quart. J. Exper. Physiol. 1923; Supplement, Proceedings XI International Physiological Congress, Edinburgh, pp. 109-110.

30. Dragstedt, L. R., and Vaughn, A. M.: Gastric Ulcer Studies, Arch. Surg. **8:** 791-810, 1924.
31. Durante, Luigi: The Trophic Element in the Origin of Gastric Ulcer, Surg., Gynec. & Obst. **22:** 399-406, 1916.
32. Edkins, J. S.: The Chemical Mechanism of Gastric Secretion, J. Physiol. **34:** 133, 1906.
33. Elman, R., and Hartmann, A. F.: Spontaneous Peptic Ulcers of Duodenum After Continued Loss of Total Pancreatic Juice, Arch. Surg. **23:** 1030-1040, 1931.
34. Eppinger, H., and Leuchtenberger, R.: Zur Pathogenese der Gastritis und des ulcus ventriculi, Ztschr. f. d. ges. exper. Med. **85:** 598-605, 1932.
35. Exalto, J.: Ulcus jejuni nach Gastroenterostomie, Mitt. a.d. Grenzgeb. d. Med. u. Chir. **23:** 13-41, 1911.
36. Fauley, G. B., Strauss, H. A., and Ivy, A. C.: Studies on the Effects of Subtotal Gastric Resection in the Dog, Am. J. Surg. **17:** 427-433, 1932.
37. Finsterer, H.: Ausgedehnte Magenresektion bei Ulcus duodeni statt der einfachen Duodenalresektion bsu. Pylorusausschaltung, Zentralbl. f. Chir. **45:** 434, 1918.
38. Flood, C. A., and Howes, E. L.: Experimental Study of the Effect of Histamine on the Healing of Gastric Defects—Artificial Gastric Ulcer, Surg., Gynec. & Obst. **58:** 136-144, 1934.
39. Friedenwald, J., Feldman, M., and Morrison, S.: The Effects of Acids and Other Substances in the Production of Acute Gastric Ulcers, J. Exper. Med. **57:** 203-213, 1933.
40. Gallagher, W. J., and Palmer, W. L.: Experimental Jejunal Ulcer—Relative Importance of Mechanical and Chemical Factors, Proc. Soc. Exper. Biol. & Med. **30:** 468-473, 1933.
41. Greggio, E.: Des ulceres gastro-duodenaux, Arch. de méd. expér. et d'anat. path. **27:** 533-590, 1916.
42. Grey, E. G.: Duodenectomy—Its Effect Upon the Life of an Animal, Surg., Gynec. & Obst. **28:** 36-42, 1919.
43. Hanke, H.: Experimentelle Erzeugung chronischer Magengeschwüre durch coffein, Klin. Wchnschr. **13:** 978-980, 1934.
44. Harde, E.: Lesions gastriques des Souris après injections repetees d'histamine, Compt. rend. Soc. de biol. **109:** 1326-27, 1932.
45. Harper, F. R.: Development of Experimental Ulcer—Changes in Acidity and Treatment, Proc. Staff Meet., Mayo Clin. **7:** 318-323, 1932.
46. Harper, F. R.: Development and Treatment of Peptic Ulcer—An Experimental Study, Arch. Surg. **30:** 394-404, 1935.
47. Hay, L. J., Varco, R. L., Code, C. F., and Wangensteen, O. H.: The Experimental Production of Gastric and Duodenal Ulcers in Laboratory Animals by the Intramuscular Injection of Histamine in Beeswax, Surg., Gynec. & Obst. **75:** 170-182, 1942.
48. Heinlein, H., and Kastrup, H.: Beitrag zur Genese der Gastritis, Ztschr. f. d. ges. exper. Med. **102:** 517-526, 1938.
49. Hoerner, M. T.: The Effect of Exclusion of the Pancreatic Juice From the Duodenum—An Experimental Study, Proc. Staff Meet., Mayo Clin. **9:** 469-476, 1934.
50. Hoffmann, A.: Experimental Gastric and Duodenal Inflammation and Ulcer, Am. J. M. Sc. **170:** 212-219, 1925.
51. Hunt, V. G.: Principles Which Govern the Extent of Gastric Resection for Duodenal Ulcer, Surg., Gynec. & Obst. **73:** 676-680, 1941.
52. Ivy, A. C.: Contributions to the Physiology of the Stomach—Studies on Gastric Ulcer, Arch. Int. Med. **25:** 6-31, 1920.
53. Ivy, A. C., Schrager, V. L., and Morgan, J. E.: Spontaneous Duodenal Ulcers in Dogs With Chronic Mild Icterus and Hepatitis, Proc. Soc. Exper. Biol. & Med. **30:** 698-700, 1933.
54. Jenkins, H. P., and Palmer, W. L.: Studies on Experimental Jejunal Ulcer, Proc. Soc. Exper. Biol. & Med. **28:** 935-936, 1931.
55. Judd, E. S., Jr.: Unpublished data, 1942.
56. Kabat, H., and Hedin, R. F.: A Nervous Factor in the Etiology of Shock in Burns, SURGERY **11:** 766-776, 1942.
57. Kanatake, Y.: The Experimental Production of Gastric Ulcer by Aliphatic Amines, J. Biochem. **27:** 405-413, 1938.
58. Kapsinow, R.: The Experimental Production of Duodenal Ulcer by Exclusion of Bile From the Intestine, Ann. Surg. **83:** 614-617, 1926.
59. Kiefer, E. D.: Jejunal Ulcers and Recurrent Hemorrhages After Partial and Subtotal Gastrectomy for Peptic Ulcer, J. A. M. A. **120:** 814-824, 1942.
60. Kim, M. S., and Ivy, A. C.: The Prevention of Experimental Duodenal Ulcer by Feeding Neutral Gastric Mucin, J. A. M. A. **97:** 1511-1513, 1931.
61. Kolouch, F.: Unpublished data, 1943.
62. Lannin, B. G., and Baronofsky, I. D.: Surgical Treatment of Ulcer, Staff Bulletin, University of Minnesota Hospitals **15:** 58-66, 1943.
63. Lannin, B. G., Hay, Lyle J., Judd, E. S., and Wangensteen, O. H.: Evaluation of a Satisfactory Operation for Ulcer, Proc. Soc. Exper. Biol. & Med. **56:** 231-233, 1944.

64. Layne, J. A., and Bergh, G. S.: The Effect of Ligation of Arteries of the Stomach Upon Acid Gastric Secretion and Upon the Endoscopic Appearance of the Gastric Mucosa in the Dog, SURGERY **13**: 136-144, 1943.
65. Light, R. O., Bishop, C. C., and Kendall, L. G.: The Production of Gastric Lesions in Rabbits by Injection of Small Amounts of Pilocarpine Into the Cerebrospinal Fluid, J. Pharmacol. & Exper. Therap. **45**: 227-251, 1932.
66. Litthauer, M.: Recherches experimentales sur la pathogenie de l'ulcers rond stomacal, J. de chir. **2**: 424, 1909.
67. Lium, R.: Peptic Ulcer and Diarrhea Following the Removal of the Prevertebral Ganglia in Dogs, SURGERY **9**: 538-553, 1941.
68. Loewy, G.: Experience sur la production d'ulceres duodenaux par derivation isolee de la bile, Bull. et mém. Soc. nat. de chir. **56**: 243-249, 1930.
69. McCann, J. C.: Experimental Peptic Ulcer, Arch. Surg. **19**: 600-659, 1929.
70. McIlroy, P. T.: Experimental Production of Gastric Ulcer, Proc. Soc. Exper. Biol. & Med. **25**: 268-269, 1927-1928.
71. McMaster, P. E.: Effects of Diverting the Gastric Contents to the Lower Intestinal Levels, Arch. Surg. **28**: 825-836, 1934.
72. Mann, F. C.: A Study of the Gastric Ulcers Following Removal of the Adrenals, J. Exper. Med. **23**: 203-210, 1916.
73. Mann, F. C., and Bollman, J. L.: Experimentally Produced Peptic Ulcers, J. A. M. A. **99**: 1576-1582, 1932.
74. Mann, F. C., and Bollman, J. L.: The Reaction of the Content of the Gastro-Intestinal Tract, J. A. M. A. **95**: 1722-1724, 1930.
75. Mann, F. C., and Kawamura, K.: Duodenectomy, Ann. Surg. **75**: 208-220, 1922.
76. Mann, F. C., and Williamson, C. S.: The Experimental Production of Peptic Ulcer, Ann. Surg. **77**: 404-422, 1923.
77. Matseuda, A.: Zur experimentellen erzeugung des Magengeschwüre durch histamin, Klin. Wchnschr. **10**: 2265, 1931.
78. Matthews, W. B.: Production of Intestinal Ulcers by Active Gastric Juice, Proc. Soc. Exper. Biol. & Med. **28**: 960-961, 1931.
79. Matthews, W. B., and Dragstedt, L. R.: The Etiology of Gastric and Duodenal Ulcer, Surg., Gynec. & Obst. **55**: 265-286, 1932.
80. Merendino, K. A.: Unpublished data, 1943.
81. Metz, M. H.: A Gastric Lesion Produced by Posterior Pituitary Extract, Texas State J. Med. **34**: 295-297, 1938.
82. Metz, M. H., and Lackey, R. W.: Treatment of Peptic Ulcer With Posterior Pituitary Extract—Preliminary Report, Texas State J. Med. **32**: 589-590, 1937.
83. Morton, C. B.: Observations on Peptic Ulcer, Ann. Surg. **85**: 207-238, 1927.
84. Morton, C. B.: Observations on Peptic Ulcer, Ann. Surg. **85**: 879-885, 1927.
85. Neuman, F., Demoor, P., and Deloyers, L.: Contribution à l'étude de la pathogenie des ulceres gastro-duodenaux, Compt. rend. Soc. de biol. **105**: 887-893, 1931.
86. Oberling, O., and Kalto, A.: Ulceres aigus de l'estomac consecutifs à des lesions experimentales des noyaux gris centraux, Compt. rend. Soc. de biol. **102**: 832-833, 1929.
87. Ochsner, A., Gage, M., and Hosoi, K.: The Relationship of Peptic Ulceration to Gastric Chemism, Proc. Soc. Exper. Biol. & Med. **31**: 1260, 1934.
88. Orndorff, J. R., Bergh, G. S., and Ivy, A. C.: Peptic Ulcer and the Anxiety Complex, Surg., Gynec. & Obst. **61**: 162-168, 1935.
89. O'Shaughnessy, L.: Etiology of Peptic Ulcer, Lancet **220**: 177-181, 1931.
90. Owings, J. C., and Smith, I. H.: Experimental Production and Cure of Jejunal Ulcers, Proc. Soc. Exper. Biol. & Med. **29**: 832-833, 1932.
91. Owings, J. C., and Smith, I. H.: Etiology of Duodenal Ulcers, Proc. Soc. Exper. Biol. & Med. **29**: 833-835, 1932.
92. Panum: Quoted by Cohnheim.[21]
93. Plenk, A.: Zur Technik der Resektion zur Ausschaltung, Zentralbl. f. Chir. **63**: 3019, 1936.
94. Reeves, T. B.: A Study of the Arteries Supplying the Stomach and Duodenum and Their Relation to Ulcer, Surg., Gynec. & Obst. **30**: 374-385, 1920.
95. Rosenow, E. C.: The Causation of Gastric and Duodenal Ulcer by Streptococci, J. Infect. Dis. **19**: 333-384, 1916.
96. Schiffrin, M. J.: Production of Experimental Jejunal Ulcer, Proc. Soc. Exper. Biol. & Med. **45**: 592-594, 1940.
97. Schmilinsky, H.: Die einleitung der gesamten Duodenalsäfte in den Magen (inner Apotheke), Centralbl. f. Chir. **45**: 416, 1918.
98. Seely, H., and Zollinger, R.: Fundusectomy in the Treatment of Peptic Ulcer, Surg., Gynec. & Obst. **61**: 161-166, 1935.
99. Shapiro, P. F., and Ivy, A. C.: Gastric Ulcer—Experimental Production of Gastric Ulcer by Local Anaphylaxis, Arch. Int. Med. **38**: 237-258, 1926.
100. Simonds, J. P.: Mode of Origin of Experimental Gastric Ulcer Induced by Cinchophen, Arch. Path. **26**: 44-50, 1938.
101. Smith, D. T., and McConkey, M.: Peptic Ulcers (Gastric, Pyloric and Duodenal), Arch. Int. Med. **51**: 413-426, 1933.

102. Stalker, L. K., Bollman, J. L., and Mann, F. C.: Experimental Peptic Ulcer Produced by Cinchophen, Proc. Staff Meet., Mayo Clin. **11**: 695-698, 1936.
103. Turck, F. B.: Ulcer of the Stomach; Pathogenesis and Pathology, J. A. M. A. **46**: 1753-1763, 1906.
104. Turck, F. B.: Quoted by Ivy.[52]
105. Underhill, F. P., and Freiheit, J. M.: Effect of Pilocarpine and Epinephrine in the Production of Specific Lesions in the Stomach of Rabbits, Arch Path. **5**: 411-428, 1928.
106. Van Wagoner, F. H., and Churchill, T. P.: Production of Gastric and Duodenal Ulcers in Experimental Cinchophen Poisoning, J. A. M. A. **99**: 1859-60, 1932.
107. Varco, R. L.: Uupublished data, 1940.
108. Varco, R. L., Code, C. D., Walpole, S. H., and Wangensteen, O. H.: Duodenal Ulcer Formation in the Dog by Intramuscular Injections of a Histamine-beeswax Mixture, Am. J. Physiol. **133**: 475-476, 1941.
109. Von Eiselsberg: Ueber Ausschaltung inoperabler Pylorusstructuren nebst BemaerKungen über die jejunostomie, Arch. f. klin. Chir. **50**: 919-939, 1895.
110. Walpole, S. H., Varco, R. L., Code, C. F., and Wangensteen, O. H.: Production of Gastric and Duodenal Ulcers in the Cat by Intramuscular Implantation of Histamine, Proc. Soc. Exper. Biol. & Med. **44**: 619-621, 1940.
111. Wangensteen, O. H.: Aseptic Gastric Resections: I. A Method of Aseptic Anastomosis Adaptable to Any Segment of the Alimentary Canal (Esophagus, Stomach, Small or Large Intestine); II. Including Preliminary Description of Subtotal Excision of the Acid-Secreting Area for Ulcer, Surg., Gynec. & Obst. **70**: 59-72, 1940.
112. Wangensteen, O. H., Varco, R. L., Hay, L. J., Walpole, S. H., and Trach, B.: Gastric Acidity Before and After Operative Procedure With Special Reference to the Role of the Pylorus and Antrum: A Preliminary Report of a Clinical and Experimental Study, Ann. Surg. **112**: 626-670, 1940.
113. Wangensteen, O. H.: Method of Closing the Pyloroantral Pouch in the Antral Exclusion Operation, SURGERY **12**: 731-741, 1942.
114. Wangensteen, O. H., and Lannin, B. G.: Criteria of an Acceptable Operation for Ulcer and the Importance of the Acid Factor, Arch. Surg. **44**: 489, 1942.
115. Wangensteen, O. H.: The Surgical Management of Ulcer: A Chemical Problem, Proc. Interst. Postgrad. M. A. North America Oct. 1942.
116. Watson, J. R.: Effect of Fundusectomy on the Acidity of the Gastric and Duodenal Content; An Experimental Study, Arch. Surg. **31**: 1-9, 1935.
117. Weech, A. A., and Paige, B. H.: Nutritional Edema in the Dog, Am. J. Path. **13**: 249-256, 1937.
118. Weiss, A. G., and Aron, E.: Role des amines dans l'evolution de l'ulcere experimental: Influence de l'histidine, Presse méd. **41**: 1880, 1933.
119. Wilensky, A. O., and Geist, S. H.: Experimental Studies in the Production of Chronic Gastric Ulcer, J. A. M. A. **66**: 1382, 1916.
120. Wolfer, J. A.: Chronic Ulcer of the Stomach: Its Experimental Production and Effect on Gastric Secretion and Motility, Ann. Surg. **84**: 89-94, 1926.
121. Wolfson, W. L., and Rothenberg, R. E.: The Surgical Treatment of Complicated Duodenal Ulcer, SURGERY **3**: 663-669, 1938.
122. Wu, P. P. T.: Reactions of Contents of Jejunum and Experimental Production of Peptic Ulcer, Arch. Surg. **30**: 557-562, 1935.
123. Wu, P. P. T.: The Effect of Histidine on the Experimental Production of Peptic Ulcer, Ann. Surg. **106**: 196-199, 1937.

REMOVAL OF THE VAGUS INNERVATION OF THE STOMACH IN GASTRODUODENAL ULCER

LESTER R. DRAGSTEDT, M.D., AND PAUL W. SCHAFER, M.D., CHICAGO, ILL.
(From the Department of Surgery of The University of Chicago)

THE capacity of pure gastric juice to digest living tissue has been demonstrated by numerous experimental studies. Although more resistant than other parts of the gastrointestinal tract, the mucous membrane of the stomach itself succumbs to the corrosive and digestant action of the fundus secretion under conditions where this secretion is not diluted or neutralized by pyloric mucus, duodenal secretions, or food.[1] It thus appears clear that under normal conditions the wall of the stomach escapes digestion because it is not exposed to the pure fundus secretion for long periods of time and not because of a special resistance to that secretion. The dilution and neutralization of the gastric juice by ingested food and drink during the periods of psychic and chemical stimulation of secretion are probably the chief factors that protect the gastric and duodenal mucosa. The importance of the continuous autoneutralization of the acid gastric juice by the duodenal secretions and the pyloric mucus has, however, been firmly established by numerous experiments. When the mixture of these secretions is prevented, progressive ulceration of the duodenum or stomach almost inevitably occurs. Thus, penetrating ulcers in the jejunum develop when the duodenal secretions are diverted into the ileum.[2] Ulcers in the jejunum, ileum, or colon occur when the gastric juice from a Pavlov or Heidenhain pouch is diverted into these areas of the intestine.[3] Ulcers in the duodenum develop when the pancreatic juice is led to the outside by means of a total fistula.[3, 4] These studies have focused attention on the necessity for more or less continuous neutralization of the fundus secretion, but so far a defect in this neutralizing mechanism has not been established as a causative factor in any large number of ulcers in man. The disease occurs chiefly in young adults without evidence of biliary or pancreatic disease or reason to suppose that these secretions are deficient.

An excessive secretion of gastric juice in the presence of normal amounts of the alkaline duodenal secretions might on theoretical grounds be expected to produce a situation similar to that resulting from deficient or absent duodenal secretions coupled with a normal gastric output. The gastric juice would finally overcome the neutralizing capacity of food and duodenal secretions and cause the appearance in the stomach and duodenum of a content approaching the pure fundus secretion in acidity and pepsin content. Evidence that such excessive gastric secretion experimentally produced in normal animals causes the appearance of typical ulcers has been provided by Wangensteen and his associates.[5] Hypersecretion was secured by implanting pellets of a mixture of histamine and beeswax into the muscles and subcu-

Work aided by a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago.
Received for publication, Oct. 16, 1944.

taneous tissues of dogs, cats, guinea pigs, and other animals and when this was continued, progressive perforating ulcers in the stomach and duodenum appeared.

That an excessive secretion of gastric juice occurs in most ulcer patients may be regarded as definitely established. Most of the data supporting this conclusion have been obtained by testing the response of the gastric glands to various types of stimulation. For the most part the stimuli employed have been chemical in nature, as for instance the Ewald test breakfast, alcohol installation, or the injection of histamine. On the whole these tests have demonstrated that ulcer patients secrete somewhat more gastric juice in response to these stimuli than do normal persons. The amount, however, is not sufficiently great or uniform to have much diagnostic value.[6] Presumably, these chemical stimuli act directly on the parietal and chief cells of the gastric glands and any increased response obtained must be due to an increased excitability or sensitivity of these cells. Unfortunately, there has been little effort to test the secretory response of the stomach in ulcer patients to psychic stimuli and to compare this response with that of normal individuals. Such information would probably be of the greatest value. A sham meal consisting of appetizing food, that is, meat, vegetables, and fruit, could be thoroughly masticated but not swallowed. If this were done while constant suction was being made on a Levin tube introduced through the nose into the stomach, the gastric juice elicited could be obtained for measurement and titration. The caffeine test meal proposed by Roth, Ivy, and Atkinson,[7] which apparently demonstrates a greater secretory response in ulcer patients as compared with normal people, probably also tests this neuroglandular mechanism. Evidence that the continuous night secretion of gastric juice in ulcer patients is greater than in normal individuals has been obtained in this clinic and has been presented elsewhere.[8]

Acting on the conception that the hypersecretion of gastric juice in gastroduodenal ulcer is very largely neurogenic in origin, a series of patients with this disease have been treated by an operation designed to remove permanently and as completely as possible the vagus innervation of the stomach. The first operations were performed in January and February, 1943, and were reported in June of that year.[9] A further report of eleven patients was made before the meeting of the American Gastroenterological Association in Chicago, June 12, 1944.[8] Since that report an additional four patients have been operated upon by the same method. It is the purpose of the present paper to discuss the operative procedure and to review the results to date.

An extensive experience with various procedures for studying gastric physiology in experimental animals suggested that the best method to secure complete division of the vagus nerves to the stomach would be to isolate these fibers in the chest before they pass through the diaphragm and enter the wall of the stomach. The desirability of such a complete operation was indicated by the studies of Hartzell.[10] This investigator found that complete division of the vagus nerves in the thorax produced a marked and long-continued decrease in the free and total acidity of the gastric content secured in response to the ingestion of a test meal of lean meat. An incomplete division had

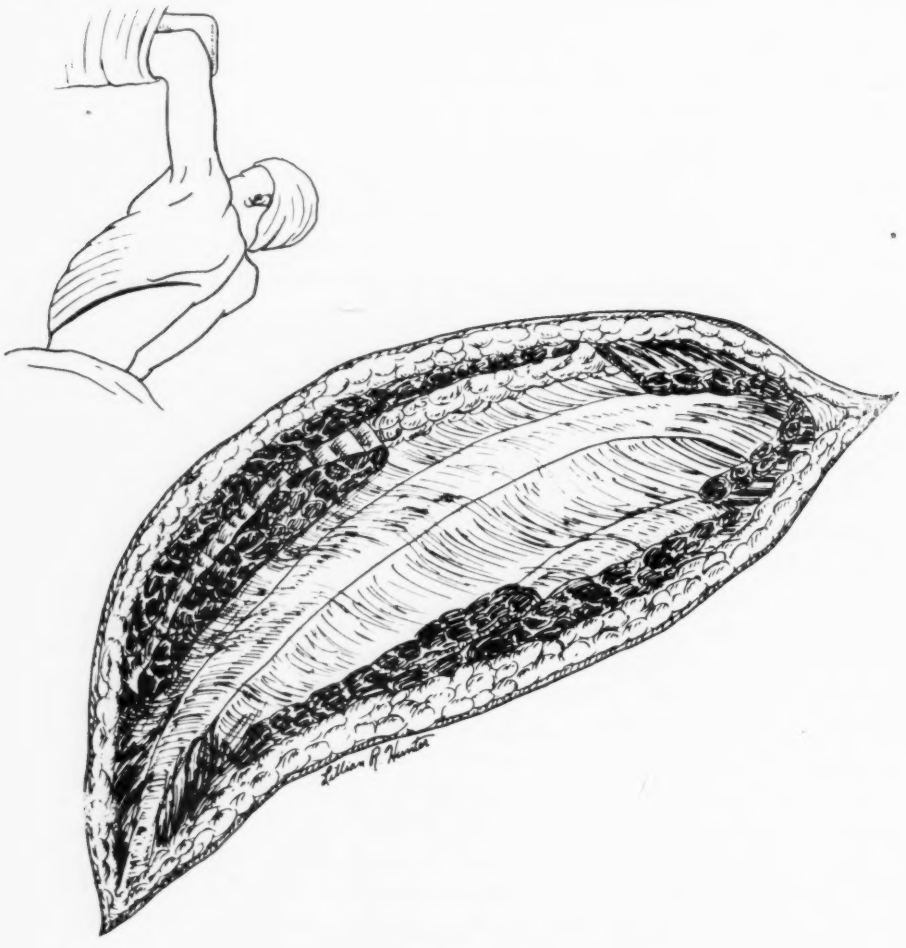


Fig. 1.

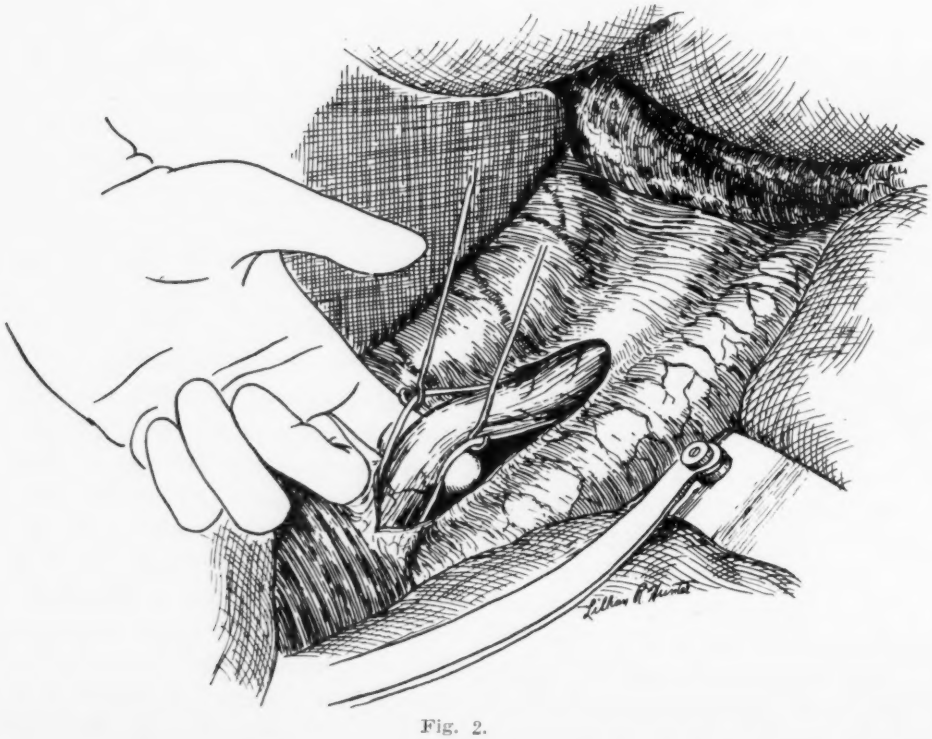


Fig. 2.

little or no effect. Data confirming and extending these observations have been secured in our laboratory by means of animals with totally isolated stomachs both with and without vagal innervation and will be reported elsewhere. The dog tolerates division of the vagus nerves low in the chest fairly well, although occasional animals vomit repeatedly and appear to have some difficulty in swallowing. The absence of adverse effects in man after excision of the lower esophagus for carcinoma, an operation which necessarily includes excision of the vagus nerves, prompted us to perform supradiaphragmatic section of the vagus nerves for the treatment of gastroduodenal ulcer.

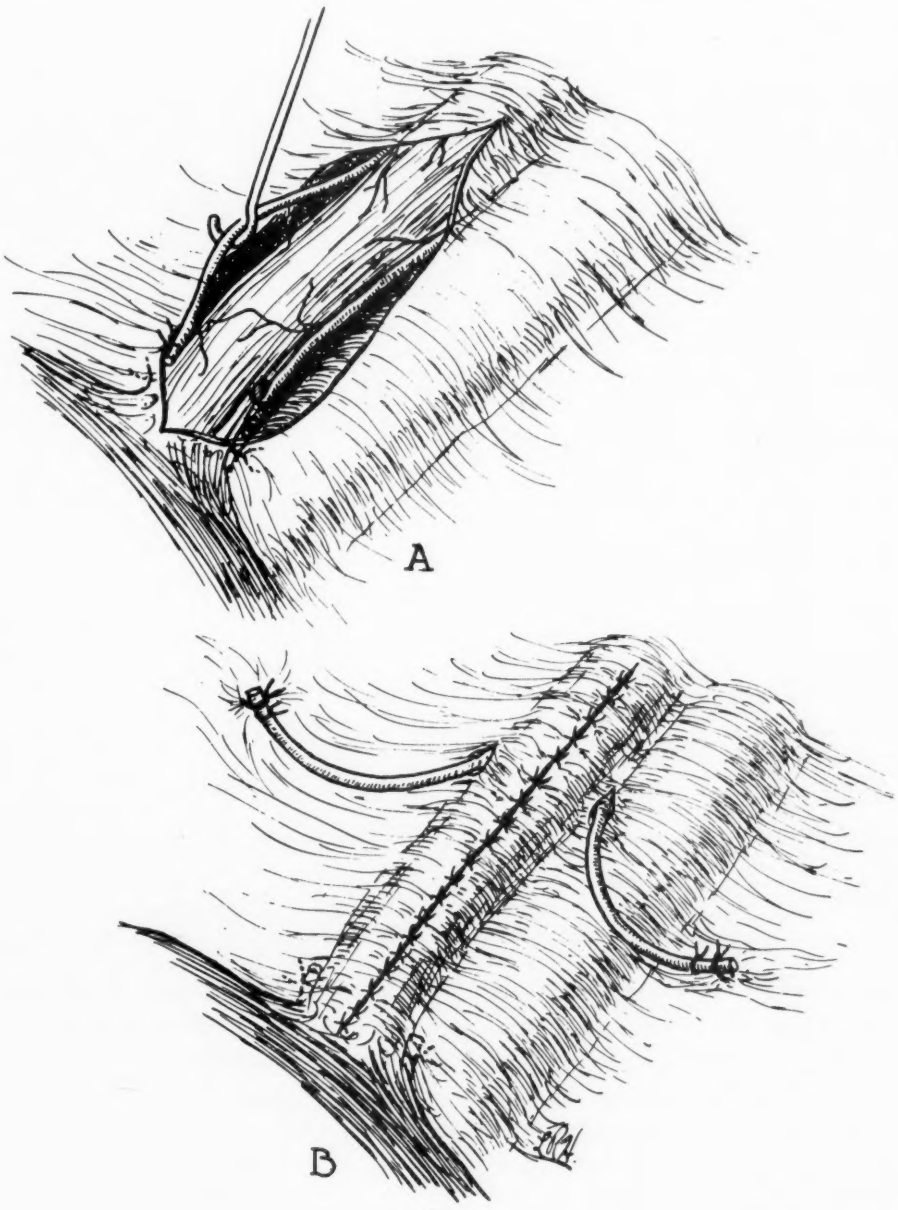


Fig. 3.

The patients were anesthetized with ethylene and ether, using a positive pressure mask technique. An extensive resection of the seventh or eighth rib on the left side was then made (Fig. 1). In the

TABLE

TABULATED SUMMARY OF DATA ON PATIENTS ON WHOM SUPRADIAPHRAGMATIC

PATIENT	AGE AND SEX	DURATION OF SYMPTOMS (YR.)	DIAGNOSIS	DIRECT VISUALIZATION OF ULCER WITH GASTROSCOPE	X-RAY EVIDENCE OF ULCER CRATER	PYLORIC STENOSIS	HEMORRHAGE	PERFORATION	VOL. PREOP. NIGHT SECRETION
W. B.	51 ♂	13	Duodenal ulcer	+	+	++	+	+	1,160
J. J. F.	40 ♂	18	Duodenal ulcer	+	+	++	++	–	1,450
M. V.	34 ♀	17	Duodenal ulcer	–	–	+	–	–	1,000
J. J.	44 ♂	13	Duodenal ulcer	–	+	+++	–	–	780
J. A.	45 ♂	5	Gastric ulcer	+	+	–	+	–	840
S. S.	54 ♂	25	Duodenal ulcer	–	+	+	++	–	1,715
C. S.	38 ♂	2	Duodenal ulcer	–	–	+	–	–	971
V. M.	31 ♂	6	Duodenal ulcer	–	+	+	–	–	1,120
J. L.	46 ♂	29	Duodenal ulcer	–	+	+	++	–	800
A. J.	47 ♂	4	Duodenal ulcer	–	+	–	–	–	1,085
E. N.	17 ♂	6	Duodenal ulcer	–	+	+	–	–	1,855
M. D.	34 ♂	12	Duodenal ulcer	+	+	+		–	
M. B.	47 ♂	6	Duodenal ulcer	–	+	++	+	+	1,020
I. C.	28 ♂	8	Gastrojejunal ulcer	–	+	–	+	–	
F. C.	40 ♂	6	Duodenal ulcer	+	+	+	+		510

earlier cases a smaller portion of rib was removed and the rib above and below fractured to facilitate exposure. A more extensive removal of rib and cartilage in later cases provided better exposure and less trauma. It is possible that a very long intercostal incision would suffice but has not been tried to date. The left lung is mobilized by dividing and ligating the inferior pulmonary ligament, retracted upward and held out of the field by a rounded broad-bladed retractor. The pleura over the lower 10 cm. of the esophagus is then opened and the lower esophagus mobilized and elevated into the field with the finger. The main trunks of the left or anterior vagus and the right or posterior vagus are easily secured. In Fig. 2, these are depicted as single nerve trunks. In most cases, however, a varying number of branches exist which can be grouped into two main bundles and ligated. In addition to the main trunks which lie alongside of the esophagus, smaller fibers of the vagi penetrate the esophageal wall. These may

I

SECTION OF THE VAGUS NERVES WAS PERFORMED FOR GASTRODUODENAL ULCER

VOL. P.O. NIGHT SECRETION	PREOP. FREE ACIDITY	P.O. FREE ACIDITY	DATE OF VAGUS SECTION	REMARKS
310	65	58	1/18/43	Complete relief of symptoms with no recurrence to 10/12/44
510	70	56	2/22/43	Complete relief, gained 40 lb in weight, no recurrence to 10/12/44
---	62	--	5/21/43	Complete relief of distress for 3 mo., then recurrence; diagnosis uncertain
250	51	11	6/15/43	Complete relief of pain but persistence of obstructive symptoms in 10/44
455	40	0	7/ 7/43	Complete relief; gastroscopy 3/27/44 showed ulcer to be healed, no recurrence 10/12/44
688	25	36	7/28/43	Complete relief with no recurrence to 10/12/44
126	69	25	11/ 3/43	Complete relief with no recurrence to 10/12/44
674	74	40	5/ 1/44	Complete relief with no recurrence to 8/44
448	48	22	5/ 1/44	Complete relief with no recurrence to 9/20/44
353	41	30	5/ 9/44	Slight relief, continued nausea and vomiting; gastroenterostomy 7/3/44, complete relief 9/20/44
425	41	21	5/24/44	Complete relief with no recurrence to 10/12/44
			6/23/44	Slight relief, continued epigastric pain and nausea; gastroenterostomy 8/2/44, complete relief to 9/2/44
215	81	42	6/26/44	Symptoms relieved for 8 wk., then acute dilatation of stomach after ingestion of large amount of food; gastroenterostomy 10/44
			6/30/44	Partial relief, frequent feeding, and alkalies required to 8/5/44
450	50	0	7/ 7/44	Fluoroscopy 8/14/44 showed disappearance of crater

be identified and combed off by elevating the esophagus with the finger. The nerve fibers then stand out as cords against the more elastic muscle tissue. All of the nerve fibers that can be detected by this combined inspection and palpation are grouped into two main bundles, ligated, and divided just above the diaphragm. In the first two cases, segments of vagus fibers 3 to 4 cm. in length were excised. In subsequent cases the nerves have been ligated, divided, and the proximal ends brought out and sutured to the pleura as indicated in Fig. 3. The esophagus is then replaced in its bed, careful hemostasis secured, and the overlying pleura closed with a running catgut suture. The transplantation of the nerves into the pleural cavity is done in an attempt to prevent regeneration. The chest is then closed without drainage. In the first five cases, a Pezzer catheter drain was introduced between the ribs and left in place for several days, but this has now been abandoned. In the early cases complete bed rest was secured for the first six postoperative days. In later cases, however, the pa-

tients have been encouraged to get out of bed for a brief period twenty-four hours after the operation, for increasing lengths of time each succeeding day, and by the fourth or fifth day are fully ambulatory. We have the impression that this early rising has many advantages and decreases the incidence and liability of pulmonary and other complications.

The results of the operation to date have been summarized in Table I. Of the fifteen patients, fourteen were males and one female. Thirteen had duodenal ulcers, one a gastric ulcer, and one a gastrojejunal ulcer. Evidence of the disease was present from two to twenty-nine years and for the most part the series represented chronic refractory disease that had persisted or recurred in spite of prolonged medical management. Serious hemorrhage had occurred in four patients, perforation in two, and craters were demonstrated in thirteen. Most of these patients secreted large volumes of highly acid gastric juice at night and this was markedly reduced by the division of the vagus nerves. The most striking result of the operation was the immediate and persistent relief of the ulcer pain and distress secured in most of the patients. This occurred so soon after operation as to suggest interruption of the sensory fibers responsible for these sensations by the vagus section. This is, however, not the sole explanation. In the patient with a gastric ulcer visualized with the gastroscope before operation, a later examination showed the ulcer to be completely healed. In eight of the patients with duodenal ulcer and in which a crater was demonstrated with the x-rays, subsequent examination by the same method indicated that the crater had disappeared. Nine of the patients gained considerable weight after the operation and in three of these the gain exceeded thirty pounds. In three patients a gastrojejunostomy was performed at varying periods after the vagus section because of persistence of obstructive symptoms and x-ray evidence of delayed emptying of the stomach. One of these patients (M. B.) is particularly instructive. This patient had a duodenal ulcer with a demonstrated crater and marked pyloric stenosis. Section of the vagus nerves produced relief from ulcer distress and for eight weeks the patient was apparently in good condition without medication or dietary restriction. Then, following the ingestion of a large amount of watermelon, he developed an acute dilatation of the stomach. When examined several days later, the dilated stomach extended to the symphysis and yielded, on aspiration, 5 L. of dark brown fluid slightly acid in reaction. Constant suction gastric drainage was then employed and subsequently a gastroenterostomy was performed. It is possible that the removal of the vagal influence with its augmentor effect on gastric tonus and motility may have played a role in the acute dilatation of the stomach in this patient. In two of the other patients a varying amount of atony of the fundus of the stomach was observed at fluoroscopy for the first week or two following the operation. In no case were symptoms suggestive of cardiospasm observed and fluoroscopic examination failed to reveal abnormalities in the function of the esophagus. Aside from the temporary gastric atony mentioned, the stomach appeared normal with respect to peristalsis, position, and tonus. No abnormalities were observed in the intestines

by x-ray and neither constipation nor diarrhea appeared. The most troublesome complication of the operation was the severe and often persistent pain in the region of the thoracotomy wound. In several cases this lasted for two to three weeks. It was probably due to tearing of the fibers of the intercostal nerve by retraction of the ribs and possibly could have been prevented by dividing or excising a portion of this nerve.

SUMMARY

Supradiaphragmatic division of the vagus nerves has been performed in thirteen patients with duodenal ulcer, in one patient with gastric ulcer, and in one with a gastrojejunal ulcer. The patient with gastric ulcer has been apparently cured of his disease as judged by the disappearance of symptoms and by x-ray and gastroscopic evidence. All but one of the patients with duodenal ulcer have been greatly improved or cured, although three patients have required gastroenterostomy because of persistence of obstructive symptoms. The patient with the gastrojejunal ulcer, although improved, has been continued on medical management. The excessive continuous night secretion of gastric juice has been markedly reduced by the vagus section thus providing additional and perhaps conclusive evidence that this abnormality is neurogenic in origin. The striking improvement in these patients is in harmony with the view that gastroduodenal ulcer is a psychosomatic disease, and that the central nervous system affects the stomach via the vagi, probably chiefly through greatly augmenting the secretion of gastric juice.

REFERENCES

1. Dragstedt, L. R.: Ann. Surg. **102**: 563, 1935; and Arch. Surg. **44**: 438, 1942.
2. Mann, F. C., and Williamson, C. S.: Ann. Surg. **77**: 409, 1923.
3. Matthews, W. B., and Dragstedt, L. R.: Surg., Gynec. & Obst. **55**: 265, 1932.
4. Elman, R., and Hartmann, A. F.: Arch. Surg. **23**: 1030, 1931.
5. Hay, L. J., Varco, R. L., Code, C. F., and Wangensteen, O. H.: Surg., Gynec. & Obst. **75**: 170, 1942.
6. Alvarez, W. C.: Gastroenterology **1**: 534, 1943.
7. Roth, J. A., Ivy, A. C., and Atkinson, A. J.: Chicago, June, 1944, American Medical Association Convention.
8. Dragstedt, L. R., Palmer, W. L., Schafer, P. W., and Hodges, P. C.: Gastroenterology **3**: 450, 1944.
9. Dragstedt, L. R., and Owens, F. M., Jr.: Proc. Soc. Exper. Biol. & Med. **53**: 152, 1943.
10. Hartzell, J. B.: Am. J. Physiol. **91**: 161, 1929.

GASTRIC ULCER AND CANCER

ARTHUR W. ALLEN, M.D.,* BOSTON, MASS.

WHEN the above title is observed, the immediate reaction many will have is that we are planning to offer evidence to support the theory of MacCarty and Broders[1] that cancer of the stomach frequently develops on chronic benign ulcer. This theory would be so difficult to prove and, in fact, would be disputed by so many pathologists that we will do no more than to state that in some ulcerative lesions of the stomach, one portion appears to be definitely benign while another section is definitely malignant. It is not necessary that we accept the possibility of malignant degeneration of chronic gastric ulcer in order to establish in our minds a sound conception of the correct management of ulcer of the stomach. One may even accept the possibility that malignancy is present in the beginning of true cancerous ulcerations and that the benign area or edge frequently observed in early cancer may be nothing more than an inflammatory extension. We are convinced that certain malignant ulcerations may behave like benign ulcer as regards symptoms and response to conservative therapy for a variable period of time only to manifest themselves as obvious cancer at a later observation. That the differential diagnosis between malignant and benign ulcer of the stomach is often difficult or in fact impossible, by the diagnostic methods at our disposal, is accepted. That radical surgery for localized cancer of the stomach appearing benign will result in a greater chance for cure than when the lesion is obviously malignant is evident.

A careful analysis of the data available for a ten-year period at the Massachusetts General Hospital showed that 14 per cent of the patients treated as having benign gastric ulcer proved to have cancer.[2] All of these lesions at the first observation gave the impression of benign ulcer. Many of these patients responded well to conservative therapy at first, losing their symptoms and regaining previously lost weight. Often the lesion appeared to diminish in size on roentgen and gastroscopic examinations. Occasionally, such an ulcer previously demonstrated by both methods was not recognizable after a month of treatment. This brought about a natural feeling of safety and therefore unnecessary delay in re-examination and the institution of radical surgery. It is difficult to explain the early behavior of some malignant ulcerations of the stomach. The improvement in symptoms and weight of the patient is easier to understand, since with bed rest and nonirritating foods, secondary inflammatory reaction is alleviated. Gastritis disappears and comfort replaces pain, gaseous eructations, nausea, and anorexia. That the actual ulceration appears to diminish in size may be due to the subsidence of inflammation about the ulcer. Possibly the crater may be leveled by granulation tissue or actually by cancer cells.

Received for publication, Oct. 5, 1944.

*Chief, East Surgical Service, Massachusetts General Hospital; Lecturer in Surgery, Harvard Medical School.

In order to arrive at a better diagnosis in the early malignant lesions, we studied our records for common factors pertaining to this group of patients. Helpful information was derived from an analysis of the location of the lesion, the age of the patient, and the duration of his symptoms. Gastric analysis, particularly as regards free acidity, and the size of the ulceration were less impressive. Data concerning the type and radiation of pain and the rate of healing with conservative therapy were of no value.

Holmes and Hampton[3] and others have shown that ulceration in the immediate 2 cm. of stomach proximal to the pylorus was prone to be malignant regardless of the size of the lesion. This was true in 65 per cent of our cases. Nearly all ulcers of the greater curvature and the fundus of the stomach are cancer. We found one ulcer in this region to be syphilitic and another that was actually benign. Ulcers involving the anterior or posterior walls proved to be cancer in 20 per cent of the cases. Lesions of the lesser curvature and those of the pylorus itself showed malignancy in 10 per cent. Inasmuch as one-half of all ulcerations of the stomach originate on the lesser curvature, we found that most of our diagnostic errors occurred in lesions of this region.

Ogilvie[4] and others have previously stressed the importance of indigestion associated with ulceration of the stomach coming on after the age of 40. In our series, we found that patients with ulcerative lesions of the stomach after middle life having had symptoms of less than one year were five times as likely to have cancer as ulcer. If, on the other hand, patients in this age group had had symptoms of five or more years, the reverse was true. Every clinician should seriously consider any patient who appeals for advice about any digestive complaint that begins after the age of 40. The diagnosis of malignancy must be ruled out by all of the aids at our disposal. If an ulcerative lesion of the stomach is demonstrated, radical therapy should be instituted as soon as suitable arrangements can be made. It is in this group particularly, that palliative measures may confuse the true issue and almost under our eyes an early curable cancer may become hopelessly inoperable. These are the victims of indigestion remedies, legally advertised in the newspapers and on the radio. Certainly a time will come when the people will demand protection against these practices. If the profession initiated proceedings against such advertising, we would doubtless have to defend ourselves on the basis of jealousy. Whatever is the best way to meet this situation, we are uncertain but there can be no doubt that hundreds of lives are lost yearly by our lax methods in this direction.

The size of the ulcer may be misleading since cancer was present in two lesions that were less than 1 cm. in diameter. On the other hand, enormous benign lesions giving the clinical impression of unfavorable cancer have been encountered. Actually, the average diameter of malignant ulcers was 2.3 cm. as opposed to 1.7 in benign lesions in our series. In all the ulcers with craters of 2 cm. in diameter, the diagnosis of cancer was established in exactly 50 per cent. It is obvious that we can only surmise that the lesion is benign if it is small

in size, if it is in one of the safer zones, if it is in younger individuals, or if it has occurred in a patient with many years of symptoms.

Free hydrochloric acid was found with equal abundance in the "ulcer-cancer" group as in those with definitely proved benign ulcer. In a parallel group of patients proved to have cancer of the stomach, 60 per cent of them showed no free hydrochloric acid on gastric analysis. We are faced, therefore, with evidence that the presence of free acid is of little help in the differential diagnosis. The absence of free acid, however, is definitely in favor of cancer.

Too much reliance has been placed on the amount of pain associated with gastric ulcerations. The common belief that pain indicates benign ulcer is erroneous. The insidious onset of many cancers of the stomach with its vague symptomatology has contributed to this fallacy. It was evident to us that many of the ulcers in our series that proved to be cancer produced pain that was relieved by food or alkalies in exactly the same manner seen in the benign group. The loss of symptoms with apparent diminution in the size of the lesion on medical treatment, in many instances of early cancer, was particularly disturbing. We are sure that patients with ulcer of the stomach should be kept under close observation. Even if an ulceration has apparently healed after one month of ideal hospital treatment, there should be a careful re-examination four to six weeks afterward. Any evidence of lack of complete healing or return of ulceration should be considered sufficient to warrant early surgery.

Deaths from cancer of the stomach are estimated to aggregate 35,000 in the United States annually.[5] Comparative studies revealed that for every two persons killed in highway accidents in this country, there were three individuals who died from cancer of the stomach. Thus far, science has not developed an effective treatment for this condition except surgery. So many patients appear for treatment in the hospital when nothing can be offered them that every effort should be made toward earlier diagnoses. Safer surgical methods have increased the operability in the past decade but the percentage of cures has remained unchanged.

Parsons[6] studied our data on an early series of gastric cancer and found that the resectability was 27 per cent and the operative mortality was 38 per cent. Later, he and Welch[7] found that resectability had increased to 37 per cent while the operative mortality was reduced to 25 per cent. The five-year respites, which included the operative mortality, had remained practically the same—20 per cent. Needless to say, in the later group, there were many added years of comfortable life. With the increase in surgical effort, there is a definite improvement in the overall results.

In our own group of questionable lesions, it was found that when resection had been done on the diagnosis of benign ulcer only to have the pathologist find that the lesion was cancer, the five-year cure rate increased to 40 per cent. With this in view, we should take a more radical attitude regarding early cancer. It is quite evident that we should include the nodal areas in our resections for all doubtful lesions. This adds little to the hazard of the operation and gives the patient his best chance for cure. It is also clear that we should more frequently do a wider resection. Often a simple total gastrectomy can be safely

done which lends itself to a better elimination of the nodal areas than many subtotal resections. This is particularly true when the lymph nodes in the region of the left gastric vessels appear to be involved. We have practiced Ogilvie's suggestion of including the great omentum in our resections for cancer for several years. It is obvious to us that this structure can be safely eliminated and no serious sequelae have resulted from its absence.

Conservative treatment of gastric ulcer is less satisfactory than it is in duodenal ulcer. Judd and Priestley[8] have reported that less than 50 per cent of patients with gastric ulcer treated at the Mayo Clinic were satisfied with medical management. In 162 patients treated by surgery, only one was unhappy with the result. In their group of patients treated for benign gastric ulcer, 10 per cent proved to have cancer.

It is not difficult to understand the confusion arising in the minds of clinicians regarding the results of conservative measures in gastric ulcer when we consider the comparative rareness of this lesion. In nearly all clinics, reports will show that duodenal ulcer occurs from seven to ten times as frequently as gastric ulcer. Duodenal lesions respond to conservative therapy in a satisfactory manner in approximately 80 per cent of the patients seen. Only those with complications or intractable pain need be treated by operation. Therefore experience in the treatment of gastric ulcer is more limited and it has taken more time to accumulate sufficient data to arrive at logical conclusions.

Subtotal gastrectomy for gastric ulcer is a safer procedure than it is for duodenal ulcer. The reason is that in gastric ulcer, the duodenum is a normal structure and presents no difficulties in a secure inversion. In duodenal ulcer, however, we are always faced with the problem of the effects of inflammation. This creates some handicap in all these cases and in nearly 25 per cent of them, a real hazard. It has taken time and experience to learn to deal with the situation safely. The mortality rate of gastrectomy for duodenal ulcer will probably always be twice that of the same procedure for gastric ulcer. In a consecutive run of sixty-five patients operated upon by the general staff at our clinic for gastric ulcer, there was one death. This was in a 76-year-old man who succumbed to coronary occlusion one week after the operation.

One should not be tempted to do palliative surgery for gastric ulcer. In a group of twenty-three patients subjected to gastroenterostomy with or without cauterization of the ulcer, there were four who died of cancer of the stomach. This shows that even experienced surgeons cannot tell by the feel or the appearance of a gastric ulcer whether it is benign or malignant.

It is interesting that anastomotic ulcer, which is the most serious and frequent late sequel to partial gastrectomy for duodenal ulcer, does not occur after the same procedure for gastric ulcer.

When one takes into consideration all these data, it seems that we have much to support the conclusion that gastric ulcer should be accepted as primarily a surgical problem. By so doing, we can be assured of a high cure rate for cancer of the stomach in those patients who really have a malignant lesion that appears to be benign. This alone offsets the slight risk associated with adequately executed surgery. Furthermore, the patient with gastric ulcer may expect relief

from his symptoms by this radical procedure and be able, with assurance, to carry his economic load in the community.

We believe that early radical surgery is indicated when a patient appears for treatment if he has an ulcer of the stomach in the prepyloric or fundal regions. If he is over 40 years of age and has had symptoms of less than one year, or if his ulcer is over 2 cm. in diameter, the same advice should be given.

If the patient is young and has a small lesion or if the ulcer is superimposed on symptoms of more than five years' duration, a more conservative attitude is justifiable. This patient should not be treated in an ambulatory fashion, as is common practice in mild or early duodenal ulcer, but should be given the benefit of an adequate hospital regimen. If the ulcer remains even partially unhealed after one month of such therapy or if there is a return of ulceration one month after healing is apparent, then this patient should be urged to submit to surgery.

Actually, when all factors are taken into consideration, this becomes a conservative attitude since it is the most logical course to pursue in our efforts to lower the annual death rate from cancer of the stomach.

REFERENCES

1. MacCarty, Wm. C., and Broders, A. C.: Chronic Gastric Ulcer and Its Relation to Gastric Carcinoma, Review of 684 Specimens, Arch. Int. Med. **13**: 208-223, 1914.
2. Allen, A. W., and Welch, C. E.: Gastric Ulcer—The Significance of This Diagnosis and Its Relationship to Cancer, Ann. Surg. **114**: 498-509, 1941.
3. Holmes, G. W., and Hampton, A. O.: The Incidence of Cancer in Certain Chronic Ulcerating Lesions of the Stomach, J. A. M. A. **99**: 905-909, 1932.
4. Ogilvie, W. H.: Cancer of the Stomach, Surg., Gynec. & Obst. **68**: 295-305, 1939.
5. Livingston, E. M., and Pack, G. T.: End Results in the Treatment of Gastric Cancer, New York, 1939, Paul B. Hoeber, Inc.
6. Parsons, L.: The Operative Curability of Carcinoma of the Stomach, New England J. Med. **209**: 1096-1101, 1933.
7. Parsons, L., and Welch, C. E.: The Curability of Cancer of the Stomach, SURGERY **6**: 327-338, 1939.
8. Judd, E. S., and Priestley, J. T.: Treatment of Gastric Ulcer, Surg., Gynec. & Obst. **77**: 21-26, 1943.

A SYNTHETIC PREDIGESTED ALIMENT FOR JEJUNOSTOMY FEEDING

FRANKLIN HOLLANDER, PH.D., STEPHAN ROSENAK, M.D., AND RALPH COLP, M.D., NEW YORK, N. Y.

WITH THE TECHNICAL ASSISTANCE OF RUTH F. KARELITZ, M.A.

(From the Gastro-Enterology Research Laboratory and the Surgical Service, The Mount Sinai Hospital)

JEJUNOSTOMY for the purpose of alimentation in a patient with obstruction of the digestive tract was first performed more than sixty-five years ago.[25] Originally, this operation was employed for feeding individuals with inoperable cancer of the stomach, but its value soon came to be recognized for various other purposes as well. It was used

The authors wish to thank Miss Henderson of the Diet Kitchen and her staff for their patient cooperation in the preparation of this material; also Mead Johnson and Co. for supplying Amigen; and Burroughs Wellcome and Co. for the Dexin used in this work.

Received for publication, Oct. 11, 1944.

(1) as a palliative procedure for feeding patients in whom oral feedings were either difficult or impossible, such as cases of inoperable obstruction of the esophagus or stomach, caused by acute inflammations or malignancies, or cases of inanition caused by pernicious vomiting of pregnancy; (2) as a preliminary procedure in extensive gastroduodenal and gastrojejunal ulceration, accompanied by marked evidence of alkalosis and refractory to medical treatment; (3) as a prophylactic measure for the relief of certain postoperative complications following surgery of the stomach, such as gastric dilatation and duodenal fistula arising from suture insufficiency, the jejunostomy being complementary (that is, made coincidentally with the major operation) or supplementary (that is, made subsequently to it); and (4) as a definitive procedure for primary gastroduodenal ulcer and for marginal ulcer secondary to gastroenterostomy—a use which was in vogue for a time, but has since lost its popularity. A detailed discussion of the numerous applications of jejunostomy is presented in a historical review of the subject, published elsewhere.[20]

Apart from its use as a palliative procedure, the most important application of jejunostomy is as an adjuvant to surgery, in order to correct certain disturbances in physiology which are attendant upon the patient's condition prior or subsequent to operation. An individual with a high obstruction of long standing, accompanied by persistent vomiting and prolonged starvation, is likely to be dehydrated, in acid-base imbalance, in negative protein balance reflected by a hypoproteinemia, and in a state of avitaminosis apart from a general state of inanition. These disturbances increase the risk of any radical operation; their preoperative correction will diminish the incidence of postoperative mortality and morbidity. Derangements in water and electrolyte equilibriums can be corrected by intravenous therapy, but loss in body weight and marked hypoproteinemia may respond only to suitable alimentation over a period of one month or six weeks. In addition to the physical improvement of the patient resulting from such feeding, there will also be a substantial improvement in the local pathologic lesions. Large gastroduodenal and jejunomarginal ulcers may be greatly reduced in size by protracted jejunal feeding. This occurs as a consequence of the simultaneous operation of several factors: (1) a reduction in the acidity of gastric contents,[13, 18, 21, 28] due to an inhibition of the secretory process, or augmentation of neutralization by regurgitated intestinal contents, or both; (2) the absence of mechanical irritation of the ulcer which occurs during oral ingestion; (3) a reduction in motor activity of the stomach, as a consequence of the frequent or continuous administration into the jejunum of a diet of high caloric value; and (4) the progressive elimination of gastric retention, by restoration of gastroduodenal continuity as the local inflammatory reaction and edema subside. Such local improvement due to a preliminary jejunostomy converts a previously inoperable condition into one in which a subtotal gastrectomy may be performed with a minimum of risk.

The value of a complementary jejunostomy in postoperative management is no less than its value as a preliminary procedure. Not only is it possible, by means of jejunal feeding, to place the patient on a high caloric and fluid intake within a short time after gastric resection or gastroenterostomy, but he can be so maintained for weeks or even months

without resorting to parenteral therapy. The efficacy of proper postoperative alimentation in ulcer patients has been objectively demonstrated by the carefully controlled, preliminary study of Mulholland, Co Tui, Wright, and Vinci.[19] In this work it was reported that the convalescence of duodenal ulcer patients, maintained postoperatively on orojejunal tube feeding of a pabulum high in amino-nitrogen, was more rapid and uneventful than that of a control group of patients not fed by tube. Furthermore, these observers found that the enteric administration of amino acids resulted in more effective utilization, as shown by nitrogen balance studies, than was obtained by their intravenous injection.

The foregoing applications and advantages of jejunostomy feeding are so striking that one wonders why the procedure has not gained wider use. There are several reasons for this. When jejunostomy was first employed, it was accompanied by certain postoperative complications: loss of intestinal contents through incompetence of the jejunal stoma, the persistence of a jejunal fistula after withdrawal of the enterostomy tube, and the frequent occurrence of intestinal obstruction due to technical imperfections associated with the Witzel type of jejunostomy. These difficulties have since been obviated by improvements in surgical technique. Another reason for the unpopularity of jejunal alimentation was the distention, nausea, vomiting, cramps, diarrhea, and enteritis, which frequently accompanied it.[20] Colp and Druckerman,[6] in a series of patients upon whom jejunostomy was performed for alimentation, reported that about 10 per cent of the patients complained of diarrhea and cramps. The nutrient material used for these cases was a standard one which had been recommended specifically for this purpose, the Scott-Ivy pabulum. It has been generally accepted that these distressing gastroenteric symptoms may be caused either by physical factors or by a group of distinctly chemical ones. Scott, Holinger, and Ivy[22] themselves comment on the great likelihood of occurrence of diarrhea and enteritis. The milder of these symptoms have been clearly associated with physical factors like the temporary engorgement of the small intestine with food material. These are easily prevented by control of the rate of drip administration, using either an efficient drip apparatus or a motor-activated pumping device such as has been described by Einhorn,[9] Mensing,[17] and Wolfer.[28] Massive feedings (that is, the periodic injection of 100 c.c. or more during a ten- to fifteen-minute interval, followed by a rest period for the remainder of one hour) are also feasible, without provoking these mild disturbances. It is essential, however, that such massive feedings be started at a lower rate than this, and be gradually increased day by day to a maximum compatible with the patient's tolerance. Following such adaptation, Stewart[24] has injected as much as 400 c.c. at one time, though it is likely that his patient was not always free of distress. Marked deviation in temperature of the dietary material from 37° C. has also been thought to be an irritant factor of significance, and many reports specify precautions on this score.

Cramps and diarrhea, however, have constituted a more serious complication and possibly a more frequent one, as evidenced by the widespread prescription of opium or similar medication. It has been generally accepted that these disturbances are caused by one or more of the

constituents of the jejunal aliment. The importance of unemulsified fat in this connection is particularly marked; attention was called to it by Busch[5] as far back as 1858, twenty years before the first surgical jejunostomy was performed. Busch employed jejunal feedings for over twenty-one weeks on a woman with a natural jejunostomy, resulting from the severance of the small bowel when a bull gored her. As a result of this mode of feeding, the patient gained twenty pounds (30 per cent) in body weight. An excessively high osmotic pressure may also be a contributing factor to jejunal irritation, since it will require considerable time for the small bowel to dilute the aliment sufficiently to prevent osmotic stimulation of the neuromuscular mechanism. These complications arising from the food material itself seem to have been a major deterrent to extensive use of a surgical procedure which is of considerable potential advantage in the management of surgical cases, and simple and safe as well. In our own observation of the routine handling of jejunostomy patients, we have repeatedly seen the abandonment of jejunal alimentation because of cramps and diarrhea, in spite of the continued need of nutritional improvement. Wangensteen, in his book on *Intestinal Obstructions*,[27] says: "The experience of this clinic suggests that the ideal formula for feeding through an enterostomy has not been found. Trial and error, with temporary periods of alimentation by the intravenous route, until the proper adjustment is made, continues to be the method that must be employed. . . ." In this same connection, Wolfer[28] states that the major proportion of previous efforts at jejunostomy feeding has been disappointing because of an inadequate understanding of the physiologic principles involved. In view of these statements and our own confirmatory experience, we have devised a new diet which conforms to the physiologic and other requirements that have been brought to light by the cumulative experience of sixty-five years of trial and tribulation.

COMPOSITION OF THE ALIMENT

For jejunal feeding, the aliment must be very easily digestible or even predigested. This is necessary because salivary and gastric digestion are completely eliminated, and pancreatic and intestinal digestion are lessened, the latter as a consequence of decreased stimulation of the corresponding glands and the reduced time of contact of these secretions with the aliment. Extensive predigestion is important also for a maximum of absorption. Wangensteen[27] pointed out that the actual caloric value of the Scott-Ivy pabulum is considerably less than the calculated value because of its incomplete digestion and consequent incomplete absorption. Scott and Ivy[21] realized this and attempted to obviate the loss by predigesting the mixture with gastric juice and pancreatin, but the product was too irritating to be tolerated. Any factors which may irritate the bowel must be excluded from an enteric aliment. Its pH should be about 6.0. Its osmotic pressure must not be too much above isotonicity, since the reduction in this property which normally results from dilution with the digestive secretions after oral feeding is greatly lessened in jejunal alimentation. In order to satisfy these requirements the various constituents of the new aliment were supplied in the following ways.

1. *Protein.*—The nitrogenous component of the enteric aliment should contain no molecules larger than tripeptides. It must, however, contain adequate amounts of the ten essential amino acids, free or combined. These requirements are met by Amigen,* an enzymatic digest of purified casein and pork pancreas which contains di- and tripeptides and amino acids (including tryptophan). McGee and Emery[16] have reported that this preparation, when placed directly into the human small intestine by the balloon intubation technique, was completely absorbed in fifteen to twenty-five minutes, whereas unhydrolyzed casein required forty to fifty minutes. The proportion of the total caloric intake derived from protein in several well-known feeding mixtures (Kirschner,[14] Scott and Ivy,[21] Walters and Hartman[26]) ranges from 6 to 16 per cent (Table I). In the predigested aliment, about 26 per cent of the total caloric intake comes from this source. Based on a daily intake of 2,400 cal. this corresponds to somewhat less than 160 Gm. of pure protein per day, or about 200 Gm. of hydrolyzed casein.† This value is far below the maximum which can be tolerated, for Brunschwig, Clark, and Corbin[4] were able to inject intravenously 150 Gm. of hydrolyzed casein per day in a 50 kg. patient for ten days without any disturbance. Also, Elman, Weiner, and Bradley[11] have injected as much as 300 Gm. per day in each of two patients without difficulty, though their observations extended for only three consecutive days.

TABLE I

COMPARISON OF SEVERAL JEJUNOSTOMY FEEDING MIXTURES WITH REGARD TO THE RELATIVE AMOUNTS OF CARBOHYDRATE, PROTEIN, AND FAT

FORMULA DEVISED BY	AMOUNT (PER LITER OF THE MIXTURE)							
	CARBOHYDRATE		PROTEIN		FAT		TOTAL	
	GM.	CAL. %	GM.	CAL. %	GM.	CAL. %	GM.	CAL. %
Kirschner*	94	376 (37)	35	140 (14)	55	495 (49)	184	1011 (100)
Scott and Ivy	81	324 (38)	35	140 (16)	43	387 (46)	159	851 (100)
Walters-Hartman								
1st day	65	260 (47)	8	32 (6)	29	261 (47)	102	553 (100)
2nd day	90	360 (44)	21	84 (10)	42	378 (46)	153	822 (100)
3rd day	97	388 (43)	25	100 (11)	46	414 (46)	168	902 (100)
6th day	101	404 (37)	33	132 (12)	63	567 (51)	197	1103 (100)
Hollander, Rosenak and Colp	152	607 (60)	66	265 (26)	16	139 (14)	234	1011 (100)

*Calculated with the aid of Sherman's tables of the caloric value of foods.

Such a high proportion of protein nitrogen is desirable, not only to prevent the further depletion of the body stores of protein, but also to replenish the tissue protein and plasma albumen previously lost by

*Manufactured by Mead Johnson and Co.

†The total nitrogen content of Amigen is given as 12.0 per cent, and this corresponds to 75 per cent of protein. Hence, to obtain 150 Gm. of protein, apart from that in the cream, we must use 200 Gm. of the hydrolyzed casein as purchased. It is usually stated, however, that 1.2 Gm. of Amigen is equivalent to 1.0 Gm. of protein, which corresponds to a protein content of 83 per cent. The discrepancy between this value and 75 per cent probably arises from the fact that the former has been calculated on the basis of a dry, ash-free preparation, instead of "as purchased." This is suggested by the following consideration. The moisture content of Amigen is given as 4.0 per cent and the total ash as 5.5 per cent; hence the nitrogen value becomes 13.3 per cent (that is, $12.0 \times \frac{100}{100 - (4.0 - 5.5)}$). Multiplying this by the usual factor of 6.25 for the conversion of nitrogen to protein, we obtain 83 per cent.

starvation and hemorrhage. Rapid regeneration of body proteins means better healing of tissues and prevention of wound dehiscence. Rapid correction of the hypoproteinemia may diminish the edematous swelling of an obstructed gastroenteric stoma or pyloric orifice. The relative amounts of amino acids utilized for the replacement of tissue and blood proteins are about 25 to 1, depending on the degree of depletion of the body and plasma stores, and the individual's ability to resynthesize the latter. Hence, only about one-twenty-sixth of the total daily intake of nitrogen is likely to be utilized by the body for the more urgent of these two purposes, the restoration of the plasma protein level, assuming that the combined intake of carbohydrate and fat is great enough to spare the amino acids from deamination.

2. *Carbohydrate.*—The requirement of predigestion for the carbohydrate constituent might be met by the use of glucose. However, Scott and Ivy,[21] Wolfer,[28] and others reported that glucose frequently causes diarrhea, probably as a result of fermentation, but that cane sugar is better tolerated. Some surgeons have recommended a reduction in sugar content for any patient in whom such difficulties are encountered; it was our aim, however, to prevent the occurrence of fermentation so that changes in composition from patient to patient will not be necessary. This end was attained by the use of Dexin,* an enzymatic digest of cereal starch, prepared with barley malt, which consists solely of dextrins (75 per cent) and maltose (25 per cent). Another advantage in the use of a starch hydrolysate is that it elevates the osmotic pressure much less than will a quantity of a simple sugar having the same caloric value. About 60 per cent of the caloric value of the aliment is derived from the carbohydrate, a proportion higher than in any of the others shown in Table I. The feeding of a large proportion of carbohydrate is of importance in order to replace the depleted glycogen stores of the liver. Furthermore, by reason of its protein-sparing action, it insures a maximum utilization of the amino acids for the building of blood and tissue proteins. Sixty per cent of carbohydrate is considerably more than is required for these purposes, but this large proportion is a consequence of the relatively small amount of fat which has been employed.

3. *Fat.*—The influence of fat in causing cramps and diarrhea has already been pointed out. Even if the motility of the small bowel is increased somewhat (though not to the extent of causing diarrhea), the consequent decrease in absorption of nutrient material may result in a loss of efficiency of utilization. Furthermore, the presence of fat in the upper part of the small intestine induces a decrease in gastric motility, as a result of enterogastrone secretion, and therefore in gastric emptying. To minimize this reaction, Wangensteen[27] recommended that the fat content be kept below two-sevenths of the total *weight* of the nutrient. Based on *caloric value*, this is equivalent to 47 per cent of the total intake, a value which roughly characterizes all of the previous mixtures (Table I). This percentage seems to us to be excessively high. Hence, the proportion of calories derived from fat in the synthetic aliment was made about one-third of this value. It was felt that predigestion of fat is not important, but it is essential that this nutrient component contain a significant quantity of unsaturated fatty acids and

*Manufactured by Burroughs Wellcome and Co.

that it can be emulsified easily. Thin cream (18.5 per cent fat content) possesses these qualifications, and it has proved satisfactory for our purpose.

4. *Inorganic Constituents.*—The inorganic requirement of a well-balanced diet is not entirely taken care of by the combined mineral content of the Amigen, Dexin, and cream. The ash content of Amigen is given as 5.5 per cent; for thin cream, 0.43 per cent; and for Dexin, 0.25 per cent; chemical analyses of the ash were available only for the first two. The deficiency in the inorganic elements, as judged by accepted standards, is made up by means of a salt mixture, the composition of which was established in the following way:

Sodium chloride: No fixed dietary standard of salt requirement can be established because of its complex physiologic relations. The normal daily intake, as calculated from the sodium and chlorine data of a survey of 150 American dietaries,[23] varied between 0.5 and 9.7 Gm. NaCl, but this was exclusive of additional table salt used as flavoring, which could not be estimated in this survey. The average for all the dietaries was 4.8 Gm. per man per day. To their jejunostomy pabulum, Scott and Ivy added 6 to 10 Gm. of NaCl per day in addition to that derived from the other constituents, but they specified that the amount must not exceed this because of the possibility of a salt edema. A 10 Gm. limit was also set by Elman and Weiner[10] as a supplement in connection with the intravenous administration of amino acids. Neither of these groups of workers, however, intended this amount of salt to compensate for an alkalosis or hypochloremia, secondary to the loss of digestive secretions. In view of the wide variability in the daily amount of saline which may be needed by surgical patients for these latter purposes, the excess requirement was not included in the salt mixture for the aliment. Instead, it was estimated for each individual case and was supplied independently of that contained in the diet, either parenterally or by jejunostomy. Hence, the total daily NaCl content of the aliment was set at 10 Gm. The salt content of the protein and fat constituents was estimated to be around 5.2 Gm. Therefore, 4.8 Gm. of NaCl per 2,400 Cal. must be added to the jejunostomy aliment by way of the salt mixture.

Potassium: The element potassium also is recognized as a dietary essential, without any estimated "requirement" being attainable. The average daily intake of the 150 American dietaries was 3.4 Gm. of potassium (range, 1.4 to 6.5 Gm.), whereas the amount of this element derived from the Amigen and cream is only 0.9 Gm. per 2,400 Cal. Hence, the daily allotment of salt mixture should include 2.5 Gm. of potassium; this is introduced in the form of KCl (4.8 Gm. per 2,400 Cal.).

Magnesium: The amount of magnesium reported in the dietary survey varied between 0.14 and 0.67 Gm. per day, with a mean of 0.34 Gm. Only about one-third of this amount is contributed by the nutrient materials of the jejunostomy diet; the balance (0.22 Gm.) is supplied in the salt mixture, in the form of the hydrated sulfate (2.2 Gm. of Epsom salts for every 2,400 Cal. of aliment).

Calcium: The Committee on Foods and Nutrition of the National Research Council has recommended a daily intake of 0.8 Gm. of calcium for all adults, except during pregnancy and lactation, when the specification is about doubled. The calcium derived from the cream

and Amigen is 0.37 Gm.; this leaves a deficit of 0.43 Gm. of calcium, which is made up by 4.8 Gm. of calcium gluconate (monohydrate, U.S.P. XI) in the salt mixture.

Iron, copper, and other metals: The National Research Council's recommendation for the daily requirement of iron in normal adults is 12 mg. Inasmuch as the Amigen alone contributes 41 mg., none of this element need be added to the salt mixture. Likewise for copper, since the 4 mg. contributed by this constituent is adequate for erythrocyte and hemoglobin formation in normal individuals. The presence of these two metals obviates, in all probability, the need for manganese and cobalt. In the event of a marked anemia, such as might result from a bleeding ulcer, additional quantities of iron and copper should be prescribed.

Phosphorus: The mean phosphorus content of the dietaries cited by Sherman varies between 0.6 and 2.8 Gm., with a mean of 1.6 Gm. per day. Therefore the quantity of phosphorus (about 2.0 Gm.) supplied by the Amigen and cream is sufficient, and no additional phosphorus need be included. However, some alkali phosphate was added to the salt mixture in order to adjust the acidity of the aliment from a pH around 5.5, which characterizes Amigen and Dexin, to a value of 6.0 to 6.5. For this purpose, 7 Gm. of secondary sodium phosphate (Na_2HPO_4, U.S.P., dried) per 2,400 Cal. was found to be sufficient.

5. *Vitamins.*—A suitable supply of vitamins is essential in general, but particularly in patients with peptic ulcer, who are likely to be markedly deficient in this respect. The daily allowances recommended by the National Research Council, Committee on Foods and Nutrition, however, make no provision for such deficits. Therefore, a minimum of twice the amounts specified for a 70 kg. male at the 2,500 Cal. level was employed for the aliment. The adjusted values are as follows: vitamin A, 10,000 IU (6 mg. β-carotene); vitamin D, 800 IU; ascorbic acid, 3,000 IU (150 mg.); thiamin, 1,000 IU (3 mg.); riboflavin, 4.4 mg.; nicotinic acid, 30 mg. These accessory factors were given in the form of halibut liver oil and a vitamin B-complex mixture,* which also contains pyridoxine and the filtrate factor. In addition to these quantities, however, the usual therapeutic doses should be administered for several days prior to the operation for jejunostomy.

6. *Calories.*—The foregoing calculations have presumed a total caloric intake of 2,400 Cal. per day. This is slightly higher than that usually recommended for a sedentary young or middle-aged man, for whom Sherman prescribes 2,000 to 2,200 Cal. The same level has been recommended for jejunostomy feeding by Wangensteen. Kirschner's[14] diet contains about 2,000 Cal. also. Walters and Hartman[26] maintained the caloric level at 1,300 from the third through the fifth postoperative day, and thereafter raised it to 2,500 Cal. by changing the proportions as well as the amounts of the several constituents. It must be remembered that a febrile reaction, following the operation, means an increased metabolism; the resultant increase in caloric requirement is usually estimated at 10 per cent per degree of fever. Based on these considerations, 2,400 Cal. was set as a daily standard for jejunal alimentation in the present work. Such feeding was started at a level much lower than this, because of bowel intolerance to large volumes of material post-

*Blexin, manufactured by International Vitamin Corp.

operatively. However, following a suitable period of adaptation, it was often possible to administer 3,000 Cal. or more per day by means of the predigested aliment.

7. *Water.*—Best and Taylor[2] state that the normal adult water requirement under ordinary circumstances is around 2,500 c.c. daily. Complete metabolism of the protein, carbohydrate, and fat in 2,400 Cal. of the predigested aliment will furnish about 300 c.c. of water. Empirically, however, we found that a final concentration equivalent to 1 Cal. per cubic centimeter was adequate for routine purposes. Additional fluid required in cases of dehydration or thirst may be supplied parenterally, immediately after the operation, or by the addition of physiologic saline solution to the aliment. A concentration as high as 1.5 Cal. per cubic centimeter was tolerated without difficulty both by dogs and by patients, but this upper level reduces the basal water intake to an undesirable extent. Furthermore, the consistency of the mixture at the lower concentration is sufficiently fluid so that clogging of the dispensing apparatus does not occur. The osmotic pressure of the aliment is substantially greater than the isotonic value, but the absence of any complications attending the use of this concentration suggests that the degree of hypertonicity is low enough to obviate excessive stimulation of bowel motility. However, this osmotic concentration factor is being given further investigation.

PREPARATION AND ADMINISTRATION OF THE JEJUNAL ALIMENT

Amounts of the amino acids, carbohydrates, and salt mixture, sufficient to make a liter of the diet (Table II) were weighed out and dissolved in warm tap water without stirring. The mixture, possessing a volume about 900 c.c.* was transferred to a milk bottle, capped, and sterilized. After cooling to below 10° C., the requisite amounts of the vitamin preparations were added, the ascorbic acid being first dissolved in a small amount of sterile water. The preparation was kept in the refrigerator until required for use, when it was warmed to about body temperature and the cream added with vigorous shaking. Scott and Ivy,[21] Bockus,[3] and others call attention to the need for warming the

TABLE II

COMPOSITION OF THE PREDIGESTED ALIMENT

	AMOUNT	
	PER LITER	PER 2,400 CAL.
Water	760 c.c.	1,824 c.c.
Amigen	85 Gm.	204 Gm.
Dexin	150 Gm.	360 Gm.
Cream (18.5 per cent; density = 1.01 at 19° C.)	85 c.c.	204 c.c.
Salt mixture*	10 Gm.	24 Gm.
Vitamins (minimum amounts)		
Halibut liver oil†	0.33 c.c.	0.8 c.c.
Blexin†	5.8 c.c.	14.0 c.c.
Ascorbic acid	63 mg.	150 mg.
*The salt mixture is prepared in the following proportions		
NaCl	100 Gm.	4.8 Gm.
KCl	100 Gm.	4.8 Gm.
$MgSO_4 \cdot 7H_2O$	46 Gm.	2.2 Gm.
Ca gluconate. H_2O	100 Gm.	4.8 Gm.
Na_2HPO_4 dried	160 Gm.	7.0 Gm. (ca.)

†International Vitamin Corp.

*As prepared in our diet kitchen, the material is made up in larger quantities than this and distributed among a number of bottles, each containing about 900 c.c. of the mixture.

material before administration. Trial experiments in this laboratory, however, have shown that the aliment is well tolerated in dogs with healthy gastrointestinal tracts, at temperatures between 20 and 40° C., provided that the rate of administration is properly controlled. However, for clinical use it is our practice to warm the material to 37° C. before placing it into the dispensing apparatus.

The aliment was administered by means of a gravity drip apparatus, provided with a needle valve at the air inlet, as described elsewhere.[7] By means of this valve, the speed of injection can be kept relatively uniform, at an average rate below 200 c.c. per hour. The cream is well emulsified and will not separate if the mixture is gently agitated by air flowing into the drip reservoir through a Mariotte tube. If the cream does separate because of interrupted use of the apparatus, it can be redistributed by gentle shaking of the reservoir. The mixture is more fluid than preparations containing starchy or mealy substances, and therefore it does not clog the rubber tube or orifices of the apparatus.

EFFICACY OF THE PREDIGESTED ALIMENT

The value of any jejunal aliment must be gauged first of all by the absence of cramps, diarrhea, and other disturbing symptoms during its administration; second, by its ability to maintain or increase body weight; and third, by its efficiency in correcting dehydration, hypoproteinemia, and alkalosis. In the present report, experimental and clinical data concerning the first two of these criteria are presented. A systematic investigation of the efficiency of the predigested diet in correcting water, electrolyte, and protein imbalances has been left for subsequent study.

Tolerance to the predigested aliment was first established by oral administration to two dogs (Dogs 131 and 142) without jejunal fistula. Both animals had lost some weight following gastric operations for other purposes, and this loss was augmented by limited food intake. They were then given the jejunal aliment by mouth, one feeding each day, for a period of thirty-eight days. Two other dogs were provided with a jejunal fistula by the Mann-Bollman[15] technique, which uses a three- to four-inch piece of ileum connecting the jejunum with the skin, to form a T type of jejunostomy. One of these animals (Dog 67) lost some weight prior to, and immediately after, the operation, before jejunal alimentation was instituted; the other (Dog 154) maintained its weight over this pre-experimental period. Jejunal feeding of the predigested mixture to the first dog was continued for five and one-half weeks, and to the second for over eight weeks. During these periods, various modifications in the conditions of feeding (quantity per day, rate of administration, temperature, etc.) were made for experimental purposes, but none of them were significant as regards body weight changes.

The quantities fed, the duration of feeding, and the weight change are indicated in Table III. The average daily intake of the diet, as presented in the last column, was calculated on the basis of the actual number of calories given the animal each day during the period of observation. In order to calculate this "per kilogram body weight," we used a "normal" weight which had been estimated from a series of weights taken prior to operation; during this preoperative period the animals had been kept on a stock diet and in excellent nutritional con-

TABLE III

SUMMARY OF OBSERVATIONS ON THE ADMINISTRATION OF THE PREDIGESTED ALIMENT

SUBJECT	METHOD OF FEEDING	DURATION OF FEEDING (DAYS)	BODY WEIGHT (KG.)				AVERAGE INTAKE OF ALIMENT† PER CAL. PER KG. PER DAY
			"NORMAL"*	MINIMUM (AT START OF ALIMENTATION)	FINAL	CHANGE (PER CENT)	
Dog 131	Oral	38	12.0	6.3	7.4	1.1 (17%)	85
Dog 142	Oral	38	14.0	10.0	10.2	0.2 (2%)	70
Dog 67	Jej.	38	10.0	8.0	8.4	0.4 (5%)	98
Dog 154	Jej.	58	11.4	11.4	12.1	0.7 (6%)	85.5
Patient 317,369	Jej.	34	68.2	55.0	61.8	6.8 (12.4%)	2,200‡

*For the dogs, this was estimated from the preoperative weight over several months. For the patient, it was based on his own estimate.

†This average was calculated on the basis of the "normal" body weight and the actual amounts given each day during the period of observation.

‡This value represents the total daily intake, and includes an average of 334 Cal. per day of milk given by intragastric drip.

dition. In this connection it should be noted that the basal metabolic rate for dogs, on the average, is estimated at 35 Cal. per kilogram body weight per day, for a 12 to 13 kg. animal.[1] However, the actual maintenance requirement, without increase of body weight, of a moderately active adult dog is usually set around 80 Cal. per kilogram per day.[8] The average caloric intake of the four dogs maintained on the predigested aliment varied between 70 and 98 Cal. per kilogram per day. At these levels the initial body weight was maintained or increased over the periods of alimentation, the response varying with the previous condition of the animal as well as the completeness of absorption of the foodstuff.

In all of the animal experiments, the concentration of the aliment was kept constant, at 1 Cal. per cubic centimeter. The jejunostomy dogs received the material by continuous drip, usually in three feedings per day. These feeding periods lasted one to two and one-half hours each, with an interval of one hour between. In Dog 67, the initial rate was 200 c.c. per hour, but this was increased to 260 c.c. on the second day. Thereafter it varied between 200 and 340 c.c. per hour. At the week end, jejunostomy feeding was discontinued and the total amount of material was fed orally. In the second animal (Dog 154) it was necessary to reduce the initial rate of drip administration to 150 c.c. per hour, because of a lower tolerance. During the third day, it was increased to 200 c.c. On the fifth day the rate was stepped up further to 250 c.c., following which it varied between this and the initial value. On the fifteenth day, the dog passed a watery stool and vomited. Episodes of vomiting occurred repeatedly for several days. There was a sudden weight loss of about 1 kg., and the experiment was discontinued temporarily. Throughout this episode, however, the stools were normal or "semiformed." The dog was kept on a bread and milk diet for the following ten days, during which time the vomiting stopped completely and 1 kg. of weight was regained. At this point jejunostomy feedings were resumed and were continued for forty days thereafter. During this second experimental period, the mode of administration was changed

from the drip to the massive injection technique, 160 c.c. being injected over an interval of fifteen minutes or less; this was repeated at hourly intervals. Oral feedings were given only during the week ends. Throughout this period no gastrointestinal disturbances occurred and the animal continued to gain in weight.

Apart from an occasional episode of loose stool in the earlier days of experimentation with Dog 67, and the one incident just referred to in Dog 154, there was never any evidence of diarrhea or abdominal pain in any of these animals. While the absence of such disturbing symptoms may be taken as a matter of course during oral feeding, their absence during the jejunostomy experiments clearly indicated that the aliment was nonirritating. The several loose stools were suspected of being associated with the presence of a contaminating organism in the aliment. Following the institution of routine daily sterilization of the drip apparatus, as well as of the aliment, this minor disturbance disappeared almost entirely. Vomiting never occurred as a consequence of oral feeding, but it was noted occasionally during the early trials of jejunal alimentation. This disturbance was clearly a consequence of an excessive rate of feeding, for it disappeared immediately when the rate was reduced. It is interesting to note, in this connection, the statement by Elman and Lischer[12] that the intravenous administration of an amino acid mixture to human beings causes vomiting when the rate exceeds 25 Gm. per hour.

Gross response of patients to the synthetic diet was established by its routine administration to eight ward patients. One of these was a jejunostomy preliminary to gastric resection; the others were complementary jejunostomies, having been performed simultaneously with subtotal gastrectomies. Two of these cases were followed more carefully than the other six, but in none of them was a systematic study made of the clinical efficacy of the new feeding mixture. The total duration of jejunal alimentation varied from six to forty-eight days, depending on the needs of the patient. The aliment was administered by the drip technique; sometimes saline solution was added, especially during the first postoperative days, when it was felt that additional water and salt were desirable. The rate of administration was always low during the first days (30 to 60 c.c. per hour) and was increased gradually thereafter to a maximum around 125 c.c. per hour. However, no systematic procedure was followed in these preliminary studies, and on occasion the drip rate was as great as 200 or even 300 c.c. per hour. Usually, the total quantity administered in twenty-four hours fell short of the goal of 2,400 Cal., because of uncontrolled variations in drip rate and intermittent discontinuance of the drip feeding, resulting from the shortage of nursing service. For this reason, some mechanical device for dispensing the material at a controlled rate is highly desirable.

All patients receiving the synthetic aliment for any significant length of time gave ample evidence of an improvement in general nutritive condition and in the chemistry of the tissue fluids. One of the two patients given special attention (No. 518919) had had a gastroenterostomy performed for an inoperable cancer infiltrating the duodenum and the head of the pancreas. During eighteen days immediately following operation, the patient was maintained on jejunal alimentation without

supplementary oral feeding, and gained seven and one-half pounds. The other (No. 517369) was a man with a history of duodenal ulcer of fifteen years' duration. An exploratory laparotomy revealed a duodenal ulcer so extensive that a subtotal gastrectomy was impossible; therefore, a preliminary jejunostomy was performed for alimentation and gastric rest. For three and one-half weeks thereafter, the patient continued to suffer violent distress and was generally uncooperative, so that although jejunal feeding was employed, it could be pursued for only part of this period and then unsystematically. By the middle of the fourth week, when his weight had dropped to the lowest observed during his period of hospitalization (121 pounds), we were able to induce a spirit of cooperation by confiding to him the investigative nature of our work. In a short time he was able to fill and control the drip apparatus himself, so that the feeding process was considerably more efficient than with any of the previous subjects. The average jejunal intake of synthetic aliment over a period of thirty-four days was about 1,850 c.c. per day; the highest single value was 4,500 c.c. per day, which appeared to be the limit of his tolerance. In addition to this, he was given about 500 c.c. (334 Cal.) of milk per day by intragastric drip, for the purpose of intragastric neutralization. Hence, his average daily intake of nutrient was almost 2,200 Cal. which resulted in a gain of fifteen pounds in weight in the course of five weeks. The pain subsided shortly after jejunal alimentation became regular. Following this period of gastric rest, a second exploration was performed, two months after the first exploratory operation. There was a striking reduction in the size of the ulcer and in the inflammatory reaction about it. A subtotal resection was performed with ease, and the postoperative course was uneventful.

Neither of these two patients experienced cramps or diarrhea, although the first had one episode of loose stools. In fact, actual diarrhea occurred in only one of the eight patients fed with the synthetic aliment (No. 518563), a patient with carcinoma of the pancreas and a functional liver impairment, who was maintained in this way for fifteen days following gastroenterostomy and jejunostomy. Twice during this period (on the fifth and sixth days) this patient experienced diarrhea, and there was a single loose stool on the eighth day and a single episode of vomiting on the eleventh. Abdominal cramps did not occur in this patient but they were reported in two others. In one of these they occurred, without any other disturbance, at the end of a ten-day period of alimentation. At this time the jejunal intake of 2,000 to 2,400 c.c. per day was being supplemented orally with a soft diet. In the second patient they occurred twice, on different days. However, one of these episodes occurred when the patient was receiving no jejunal alimentation at all; the second episode occurred at the end of a three-day period of distention and vomiting, during which the jejunal intake was never greater than 840 c.c. per day. The succeeding six days were unaccompanied by vomiting, cramps, etc., even though the intake on one of these days was greater than 2,600 c.c. Consequently, the disturbances on both these days must be attributed to a cause other than the composition of the jejunal aliment. Vomiting, in association with jejunal feeding, occurred once with each of two patients, and four times (on two suc-

cessive days) with a third, but these symptoms disappeared as soon as the rate of administration was reduced to a more tolerable level. Subsequent gradual increase of the rate of drip was always well tolerated, and some of our patients were able to take as much as 300 c.c. per hour with no reaction worse than a feeling of fullness. This is consistent with our dog experiments, in which as much as 340 c.c. per hour was administered without untoward effects.

DISCUSSION

Our major problem in the present work was to develop a nutritionally adequate diet for jejunal alimentation which could be tolerated without the disturbing gastrointestinal symptoms which have attended the use of previous formulae for this purpose. An analysis of the factors which are important in the composition of such an enteric aliment indicated that it must be nonirritating and very easily digestible or predigested. This calls for a suitable adjustment of the pH of the nutrient material, avoidance of an excessively high osmotic pressure, and the omission of fruit juice as a source of vitamins. The daily caloric intake should be high enough to effect an increase in body weight. The calories must be distributed among the major nutritive elements in such a way that the proportion of protein calories is fairly high and fat calories low. Previous workers recognized the need for a low fat intake in order to prevent the cramps and diarrhea, but in spite of this, several well-known enteric feeding mixtures contain a very high proportion of calories from this source. Furthermore, the fat must be supplied in a well-emulsified form; thin cream has been found excellent for this purpose. As for the protein, a mixture of amino acids and simple polypeptides afforded an adequate degree of predigestion without sacrifice of any of the essential amino acids. As a source of carbohydrate, glucose must be excluded because its fermentation may cause diarrhea. The use of cane sugar alone is also undesirable, because it would result in an excessive elevation of osmotic pressure. In the present work, a mixture of maltose and dextrins proved to be satisfactory. Provision must be made for all the essential vitamins and minerals, especially an adequate supply of NaCl to maintain water and salt balance, and of iron and copper for hemoglobin formation. If avitaminosis, alkalosis, anhydremia, or anemia are present, the jejunal supply of these factors must be supplemented parenterally or by the jejunal route. Proper sterilization of the aliment (before the addition of the vitamins) and of the drip apparatus is a factor of considerable magnitude in relation to the prevention of a possible enteritis. And finally, proper control of the rate of administration is of paramount importance. Unless the feeding is slow enough, the aliment may cause nausea and vomiting. For this reason, a satisfactory jejunal aliment must be of fairly thin consistency, so as to ensure a more or less even flow of material from the drip apparatus into the jejunum. A mechanical dispenser is to be preferred to a drip apparatus, but as yet we have been unable to obtain one for our purpose.

After several experimental mixtures had been tried, a preparation was finally evolved which conformed with these requirements. This synthetic predigested aliment was then given to dogs, by the oral and jejunal routes, in order to study its efficacy in regard to maintenance of

body weight, and its freedom from irritating elements. Detailed study of two surgical patients and routine ward observations on six others confirmed clinically our experimental observations on animals. At no time was there a permanent weight loss, and an increase was observed frequently. Nausea and vomiting occurred a number of times in association with jejunal feeding, but invariably they were traced to an excessive rate of administration, and disappeared with its adjustment. A maximum drip rate as high as 300 c.c. per hour was attained clinically, which appeared to be near the limit of tolerance for these patients, but a rate of about one-half of this is sufficient when administration is more or less continuous. However, immediately after operation, jejunal alimentation should be started at a low rate, preferably around 60 c.c. per hour. The speed with which this can be increased depends on the reactions of the individual patient, but after a five-day period of adaptation, a rate of 150 c.c. per hour may be attained. To introduce 2,400 Cal. under these conditions, not more than sixteen hours are required. This rate of administration presumes that no physiologic saline solution is added to the nutrient material. When such addition is necessary, especially during the first few days postoperatively, it is generally made by substituting the salt solution for an equal volume of the aliment. Diarrhea in association with jejunal feeding was encountered in only one of the eight patients, and cramps in two of them, but there was good reason to believe that these disturbances were unrelated to the predigested aliment.

It must be recognized that the disturbing symptoms which may result from inadequacies in composition of the aliment, or in the conditions of its administration, may occur also as a result of other factors specifically associated with the patient's condition. Nausea, vomiting, abdominal pain, and cramps complicate practically every major abdominal operation during the first five days postoperatively. These may occur even after the ingestion of tea or other fluids. It is difficult, therefore, to evaluate properly the role of the jejunal aliment itself in the occasional causation of these symptoms. Nevertheless, there is ample evidence that the synthetic predigested mixture employed in these studies does not induce these gastrointestinal disturbances if it be properly administered. The value of any enteric feeding mixture depends also upon the efficiency of its absorption and utilization by the body. The adequacy of this new aliment in this regard also has been demonstrated both experimentally and clinically by the maintenance or gain of body weight in all instances in which it was used. The evidence from this preliminary investigation, therefore, has justified the routine clinical use of this new enteric aliment.

SUMMARY

The clinical uses of jejunal alimentation are briefly reviewed. Reasons for the current lack of widespread use of this feeding procedure are analyzed, in relation to the physiologic factors concerning the composition of the nutrient material. On the basis of these factors, the formula for a synthetic predigested aliment is presented, together with the method of its preparation. In contrast with previous formulas, emphasis is laid upon the incorporation of predigested proteins, the marked reduction in the fat content, the use of partially predigested carbohy-

drate free of hexose sugars, and the liberal supply of essential salts and vitamins. Evidence for the efficacy of this nutrient mixture is based on increase in body weight and absence of cramps and diarrhea, specifically associated with its administration to experimental animals and patients with jejunostomy. Furthermore, it has been shown that the occasional occurrence of untoward symptoms like nausea, vomiting, and distention can be eliminated by starting the rate of feeding at 60 c.c. per hour and gradually increasing it to a maximum of 150 to 200 c.c. per hour about the fifth postoperative day, the speed of increase and the upper limit being established for each patient individually. The importance of sterilization of the aliment and the drip apparatus is also discussed. This preliminary investigation, therefore, has justified the clinical use of this synthetic predigested aliment, and the response of a larger group of cases to its administration is now being studied.

REFERENCES

1. Benedict, F. G.: Vital Energetics: A Study in Comparative Basal Metabolism, No. 503, Washington, D. C., 1938, Carnegie Institution of Washington.
2. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 3, Baltimore, 1943, Williams & Wilkins Company.
3. Bockus, H. L.: J. A. M. A. **82**: 351, 1924.
4. Brunschwig, A., Clark, D. E., and Corbin, N.: Ann. Surg. **115**: 1091, 1942.
5. Busch, W.: Virchows Arch. **14**: 140, 1858.
6. Colp, R., and Druckerman, L. J.: Ann. Surg. **117**: 387, 1943.
7. Cornell, A., and Hollander, F.: Rev. Gastroenterol. **9**: 354, 1942.
8. Cowgill, G. R.: J. Biol. Chem. **56**: 725, 1923.
9. Einhorn, M.: Med. Rec. **78**: 92, 1910.
10. Elman, R., and Weiner, D. O.: J. A. M. A. **112**: 796, 1939.
11. Elman, R., Weiner, D. O., and Bradley, E.: Ann. Surg. **115**: 1160, 1942.
12. Elman, R., and Lischer, C.: Internat. Abstr. Surg. **76**: 503, 1943.
13. Henning, N.: Arch. f. Verdauungskr. **41**: 321, 1927.
14. Kirschner, M.: Arch. f. klin. Chir. **157**: 561, 1929.
15. Mann, F. X., and Bollman, J. L.: Ann. Surg. **93**: 794, 1931.
16. McGee, C., and Emery, Jr., E. S.: Proc. Soc. Exper. Biol. & Med. **45**: 475, 1940.
17. Mensing, E. H.: Wisconsin M. J. **32**: 168, 1933.
18. Mensing, E. H., and Kelley, E. H.: Am. J. Surg. **20**: 99, 1933.
19. Mulholland, J. H., Co Tui, Wright, A. M., and Vinci, V. J.: Ann. Surg. **117**: 512, 1943.
20. Rosenak, S., and Hollander, F.: Clinics **1**: 638, 1944.
21. Scott, H. G., and Ivy, A. C.: Ann. Surg. **93**: 1197, 1931.
22. Scott, H. G., Holinger, P. H., and Ivy, A. C.: Proc. Soc. Exper. Biol. & Med. **28**: 569, 1931.
23. Sherman, H. C.: Chemistry of Food and Nutrition, Ed. 6, New York, 1941, The Macmillan Company.
24. Stewart, J. D.: Ann. Surg. **96**: 225, 1932.
25. Surmay: Bull. gén. de thérap. **94**: 445, 1878; Ibid. **95**: 198, 1878.
26. Walters, W., and Hartman, H. R.: Arch. Surg. **40**: 1063, 1940.
27. Wangensteen, O. H.: Intestinal Obstructions, ed. 2, Springfield, Ill., 1942, Charles C Thomas.
28. Wolfer, J. A.: Ann. Surg. **101**: 708, 1935.

Editorial

Peptic Ulcer

A SYMPOSIUM on peptic ulcer is always timely, because ulcers of the stomach and duodenum are so frequently encountered and because of the likelihood of their recurrence. Generally, it is important to differentiate between an ulcer of the duodenum and one of the stomach, because it is quite universally accepted that the former is primarily a medical problem, whereas the latter is largely a surgical one. The reason for the differentiation between the two types is the susceptibility of the gastric mucosa to malignant change and the possibility either of a benign ulcer's becoming malignant or of the ulcer's masking an underlying malignant change.

There are many factors which are responsible for the development of peptic ulceration, one of the most important of which is a constitutional predisposition which is inherent in the individual and which he possesses for his entire life. For this reason, it is imperative in the handing of an ulcer patient to have him change his mode of living for the rest of his life in such a way that the precipitating factors responsible for the production of an ulcer are obviated. Of the precipitating factors, unquestionably hyperacidity is the most important. This is substantiated by the fact that the various methods of therapy which are employed, with few exceptions, either prevent or control gastric acidity. Although the healing of an uncomplicated peptic ulcer usually offers no difficulty, unfortunately too few physicians appreciate the importance of the prevention of its recurrence, which is possible only with a rational understanding by the patient that he must avoid those factors which produce increased acidity. Whereas the detrimental effects of alcohol and tobacco have been known for some time, the importance of refraining from the use of these substances after the ulcer has healed is not sufficiently realized by the medical profession generally. The detrimental effect of caffeine to patients who have an ulcer diathesis has not been emphasized until relatively recently. The investigations of Ivy and his associates and of Merendino and his associates clearly indicate the necessity of abstaining from the use of caffeine-containing drinks by the ulcer patient. The psychic factor in the production of ulcer is a prominent one. Although more difficult to define than the role which gastric acidity may play, it is a well-known fact that a patient with an ulcer is frequently relieved of all of his symptoms the moment he goes on a vacation even though he may disregard his dietary regimen entirely.

In the treatment of an active ulcer, antacids as well as frequent feedings, both of which tend to neutralize the acidity, are of value. Of importance also is the use of antispasmodics in order to favor the reflux of the alkaline duodenal secretion into the stomach by overcoming pylorospasm. Frequently the use of continuous drip is essential in the control of the ulcer as emphasized by the results of Winkelstein and his associates.

As emphasized here, treatment of the acute ulcer is not difficult. Generally, and usually within a few weeks, the ulcer will heal completely. Too frequently, however, the physician is likely to discharge his patient without emphasizing to him the necessity of his avoiding those factors which cause hyperacidity and which will result in the recurrence of the ulcer. In outlining such a therapy, it is not necessary to have the patient lead the life of an invalid. As a matter of fact, simply by eating frequently, by avoiding overeating at any time for the rest of his life, and by avoiding smoking and drinking and the use of condiments, he will be able to remain comfortable without exacerbations of the ulcer.

The surgical treatment of ulcer of the duodenum is largely that of complications, there being a few cases of intractability of the ulcer which will not respond to medical therapy in which a surgical procedure is justified and which is necessary to bring about relief. It is the consensus at the present time that when surgery is indicated in the treatment of peptic ulcer, a radical procedure is necessary. Gastrojejunostomy should be done seldom in the treatment of peptic ulcer and is indicated only in the case in which, because of a long-standing cicatricial stenosis of the duodenum or the pylorus, there has resulted an atrophic gastritis with its concomitant hypochlorhydria and achlorhydria. The danger of the development of a jejunal ulcer in a patient with a hyperacidity is far too great to justify a gastrojejunostomy in such a case. Although there is some difference of opinion concerning the amount of stomach that should be removed in doing a partial or subtotal gastrectomy for peptic ulcer, there is general agreement that all of the pylorus and the pyloric antrum must be removed. As repeatedly emphasized by Wangensteen and demonstrated conclusively by the work of Lannin, massive resections are essential, and it is also important that as short an intestinal loop be used to make the anastomosis as possible in order to insure against the recurrence of an ulcer.

In gastric ulcer, one should always suspect the possibility of malignant change or the coexistence of a neoplasm with ulceration. For this reason, a gastric ulcer which does not heal completely within a short period of time should be resected, because the best time to treat gastric carcinoma is at the time when the diagnosis cannot be made.

—*Alton Ochsner, M.D.*
New Orleans, La.

Announcement

In compliance with the directives imposed by the War Production Board limiting the amount of paper consumed in the production of this JOURNAL, the publishers find it necessary to change the format. As soon as these restrictions are lifted the original format will be restored. Even though the number of pages has been reduced, the actual content of the journal has not been decreased to any appreciable extent.

Books Received

The receipt of books is acknowledged in this section and this treatment must be regarded with sufficient acknowledgment of the courtesy of the senders. Selections will be made for more extensive review dictated by the interests of our readers and as space permits.

SURGERY OF THE HAND. By Sterling Bunnell, M.D., Honorary Member of American Academy of Orthopedic Surgeons. Cloth. Price $12. Pp. 734, with 597 illustrations. Philadelphia, 1944, J. B. Lippincott Company.

AN OUTLINE OF TROPICAL MEDICINE. By Otto Saphir, M.D., Professor of Pathology, University of Illinois College of Medicine. Cloth. Pp. 86. Chicago, 1944, The Michael Reese Research Foundation, Publisher.

PRINCIPLES AND PRACTICES OF INHALATIONAL THERAPY. By Alvan L. Barach, M.D., Associate Professor of Medicine, Columbia College of Physicians and Surgeons. Cloth. Price $4. Pp. 315, with 59 illustrations. Philadelphia, 1944, J. B. Lippincott Company.

A METHOD OF ANATOMY (DESCRIPTIVE AND DEDUCTIVE). By J. C. Boileau Grant, M.C., M.B. Ch. B., Professor of Anatomy in University of Toronto. Cloth. Price $6. Pp. 822, with 750 illustrations. Baltimore, 1944, Williams & Wilkins Company.

TÉCNICA CIRURGICA ABDOME, 2 vol. By Alfredo Monteiro, University of Brazil. Cloth. Pp. 1205, with 1248 illustrations. Rio de Janeiro, 1943, Editora Scientifica, Publisher.

CINEPLASTIC OPERATIONS ON STUMP OF THE UPPER EXTREMITY. By Rudolf Nissen, M.D., and Ernst Bergmann, M.D., New York, N. Y. Cloth. Pp. 88. New York, 1942, Grune & Stratton, Inc.

ENDOCRINOLOGY OF WOMAN. By E. C. Hamblen, B.S., M.D., F.A.C.S., Clinical Professor of Endocrinology and Associate Professor of Obstetrics and Gynecology, Duke University, School of Medicine, Durham, N. C. Cloth. Price $8. Pp. 571, with 157 illustrations. Springfield, Ill., 1945, Charles C Thomas, Publisher.

THE WOMAN ASKS THE DOCTOR. By Emil Novak, M.D., Associate in Gynecology, Johns Hopkins Medical School. Cloth. Price $1.50. Pp. 130, with 11 figures. Baltimore, 1944, Williams & Wilkins Company.

AIDS TO ORTHOPOEDIC SURGERY AND FRACTURES. I. E. Zieve, M. A. Capetown, Surgical Registrar, Charing Cross Hospital; Temporary Assistant Orthopoedic Surgeon to Royal Waterloo Hospital, London. Cloth. Pp. 270. London, 1944, Baillière, Tindall & Cox.

AMERICAN MEDICAL PRACTICE IN THE PERSPECTIVES OF A CENTURY. By Bernhard J. Stern, Ph.D., Lecturer in Sociology, Columbia University, Visiting Professor of Sociology, Yale University. Cloth. Price $1.50. Pp. 156. New York, 1945, Commonwealth Fund.

MEDICAL USES OF SOAP—A SYMPOSIUM. Edited by Morris Fishbein, M.D. Cloth. Price $3. Pp. 182, with 41 illustrations. Philadelphia, 1945, J. B. Lippincott Company.

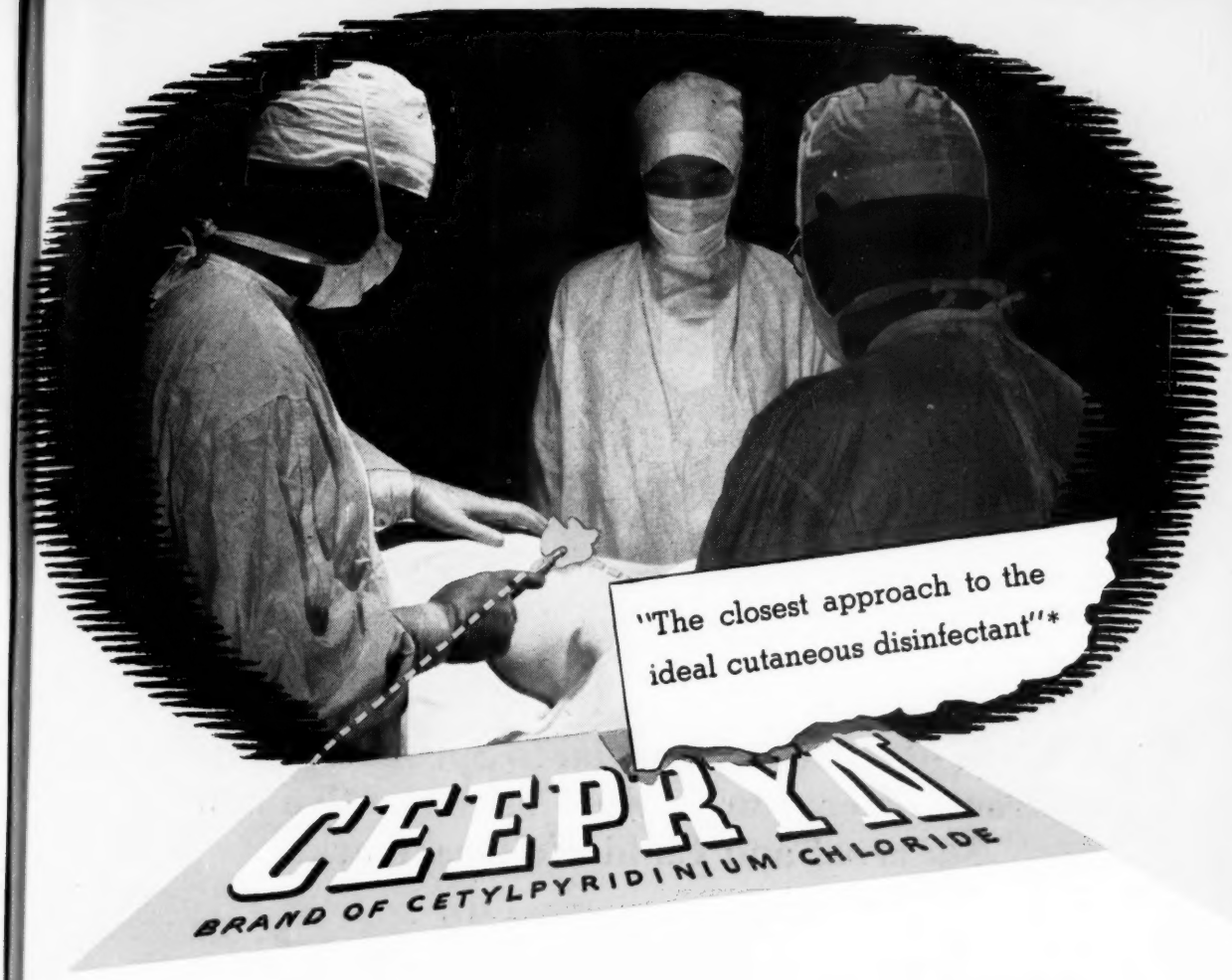
PRACTICAL ANAESTHETICS. By J. Ross MacKenzie, M.D., Lecturer on Anaesthetics, University of Aberdeen. Cloth. Pp. 136, with 63 illustrations. Baltimore, 1944, Williams & Wilkins Company.

TEXTBOOK OF SURGICAL TREATMENT—INCLUDING OPERATIVE SURGERY. By C. F. W. Illingworth, M.D., Regins Professor of Surgery, University of Glasgow. Cloth. Pp. 564, with 230 illustrations, Baltimore, 1944, Williams & Wilkins Company.

SHOULDER LESIONS. By H. F. Moseley, M.A., D.M., F.R.C.S., F.A.C.S., 301-327 East Lawrence Avenue, Springfield, Ill. Cloth. Price $4.50. Pp. 181, with 70 illustrations. Springfield, Ill., 1945, Charles C Thomas, publisher.

ARTERIAL HYPERTENSION: ITS DIAGNOSIS AND TREATMENT. By Irvine H. Page, M.D., and Arthur Curtis Corcoran, M.D., Research Division of Cleveland Clinic Foundation, Cleveland, Ohio. Cloth. Price $3.75. Pp. 352, with 13 illustrations. Chicago, 1945, The Year Book Publishers, Inc.

SURGERY OF MODERN WARFARE, Vol. 1 and 2. Edited by Hamilton Bailey, F.R.C.S., C. Allan Birch, M.D., M.R.C.P., D.C.H., D.P.H., M.M.S.A. Cloth. Pp. 1108, with 1128 illustrations. Baltimore, 1944, Williams & Wilkins Company.



In these words the authors* describe their experience with Ceepryn, following extensive bacteriological and clinical studies covering 18,000 surgical cases.

". . . Ceepryn seems to be of particular value because of its combination of high germicidal activity and detergence . . . There has been no instance of irritation, and there have been evidenced no idiosyncrasies to the drug. . . . Ceepryn is, in our experience, the closest approach to the ideal cutaneous disinfectant that we have been able to find."

CEEPRYN

The Surgeon's Antiseptic

POTENT • DETERGENT • NEGLIGIBLE TOXICITY

Ceepryn Concentrated Solution 10.56%—for preparing solutions and tinctures of any desired strength—180 cc., gallons.

Ceepryn Tincture 1:200 (Tinted)—4 oz., pints, gallons.

Ceepryn Tincture 1:500 (Tinted and Untinted)—4 oz., pints, gallons.

Ceepryn Aqueous Solution 1:1000—pints, gallons.

Write for literature

*Kramer, G. B., and Sedwitz, S. H.: Ceepryn clinical and bacteriological studies, Am. J. Surg. 63:240-245 (Feb.) 1944.

MERRELL
117 th Year

Trademark "Ceepryn" Reg. U. S. Pat. Off.

THE WM. S. MERRELL COMPANY · CINCINNATI, U. S. A.

Authoritative — Up-to-the-Minute — Complete

CURRENT OBSTETRICS AND GYNECOLOGY

Proceedings of the Second

AMERICAN CONGRESS ON OBSTETRICS AND GYNECOLOGY

A correlated program of essays, panel discussions and symposia epitomizing everything important and new in the fields of obstetrics and gynecology. The subject material, carefully integrated in advance, is presented under the strict criteria of question and answer discussions. Authors are unimpeachable authorities—each in his respective field. Discussors are especially selected for experience, critical ability. Analyses and summaries are—as a result—the last word. No stone is left unturned. The result is:

A Work Absolutely Essential to Specialist, General Practitioner, Nurse, Hospital Executive and Maternal and Child-Welfare Worker

Among the Contributors Are:

Fred L. Adair	Nicholson J. Eastman	Edward Allen
Aura E. Severinghaus	Herbert E. Schmitz	Robert D. Mussey
Robert Latou Dickinson	E. D. Plass	J. P. Greenhill
G. D. Royston	I. C. Rubin	E. G. Waters
Carl G. Hartman	Abner I. Weisman	Harry W. Mayes
R. S. Siddall	David S. Hillis	Alan F. Guttmacher
John L. Parks	Lewis C. Scheffey	Philip Levine
Alex E. Brown	A. W. Diddle	A. N. Arneson
E. Granville Crabtree	James R. Reinberger	Sidney O. Levinson
Curtis J. Lund	Lyman W. Mason	Paul F. Fletcher

and over sixty others

| *Almost every important teaching institution represented.*

|| *Obstetrics, Gynecology, Obstetrical Hospital Management, Obstetrical Nursing, Public Health and Social Service Aspects.*

||| *A complete correlated refresher course absolutely up to date.*

Price, $5.50

PUBLISHED BY THE WESTERN JOURNAL OF SURGERY PUBLISHING COMPANY, PORTLAND, OREGON, FOR THE AMERICAN CONGRESS ON OBSTETRICS AND GYNECOLOGY

To: 5-45

THE AMERICAN CONGRESS ON OBSTETRICS AND GYNECOLOGY
650 Rush Street
Chicago, Illinois

Please place my order for one copy of the 1942 Transactions, at $5.50 per volume, for which check is enclosed (or) you may bill me when volume is shipped.

Name _____ M.D.

Address _____ City _____ State _____

"Surgeons Owe a Debt of Gratitude"—*Surgery*

Feldman: CLINICAL ROENTGENOLOGY of the DIGESTIVE TRACT (*New 2nd Edition*)

By **MAURICE FELDMAN, M.D.**, Assistant Professor of Gastro-Enterology, University of Maryland; Associate Roentgenologist, Sinai Hospital; Assistant in Gastro-Enterology, Mercy Hospital, Baltimore. Second edition, 1945, 778 pages, 551 illustrations, $7.00.

Dr. Walter C. Alvarez truly described the first edition as "a monumental work which covers well every phase of the roentgenology of the digestive tract." It has been found an extremely useful and practical guide to prompt and accurate diagnosis, not only by radiologists and specialists in gastro-enterology but by a large army of internists, surgeons and general practitioners. The author has been very thorough in assembling and digesting the vast literature and writes from the fullness of an extensive experience in the special field. In bringing this new edition up-to-date many new chapters and 190 illustrations have been added. Much unessential data have been eliminated, including tables. There is a reduction of 250 pages and three dollars in price. You will find a copy of the new edition a profitable investment for civilian or military practice.

READ THESE EXCERPTS FROM REVIEWS

"This is a monumental work which covers well every phase of the roentgenology of the digestive tract. It is well and interestingly written and few words are wasted. All roentgenologists will want to have a copy within reach, and all of us who are interested in gastro-enterology have been placed in Dr. Feldman's debt." Dr. Walter C. Alvarez (Mayo Clinic) in *American Journal of Digestive Diseases.*

"This book covers completely the whole subject of roentgenology of the gastrointestinal tract. It represents a tremendous amount of work on the part of the author. Each disease described has its clinical side presented sufficiently to allow both the clinician and the roentgenologist to obtain a fairly complete picture of the whole subject. The book is well written, has a large index, and can be recommended for the use of clinicians and roentgenologists." *Journal A. M. A.*

"Throughout the volume Dr. Feldman discusses not only the roentgenological considerations of disease of the gastro-intestinal tract but also the clinical, surgical, and pathological aspects. The book will be appreciated particularly by roentgenologists and gastro-enterologists but is recommended to any student or physician who wishes to learn more about the diagnostic roentgenology of the digestive tract. The book is well written, is characterized by its completeness, and is recommended without reservation." *Surgery, Gynecology and Obstetrics.*

"This book is crammed with valuable information. It is the only volume of its kind in all English medical literature, representing a lifetime of work and study into the many problems confronting us in application of the X-ray to clinical investigation of the digestive tract. The material is well written and the illustrations excellent. No library of individual, school, college or hospital can be considered to be complete without a copy of this book on its shelves." *New York State Journal of Medicine.*

"It is a book essential alike for the roentgenologist and gastro-enterologist, as well as to the internist who, not satisfied merely to accept the reports of others, wishes to satisfy himself about the interpretation of a series of gastro-intestinal films. A diligent study of this book will serve as an excellent preparation for one who intends to specialize in this field." *Review of Gastro-enterology.*

"The volume will serve as a text and with the diagnosis of diseases of the gastro-intestinal tract." *American Journal of Roentgenology.*

"This is a most commendable text, written from the viewpoint of a clinician, that contains a wealth of information which is pertinent to the successful pursuit of an important specialty of medicine." *Radiology.*

"This unusual monograph will fill a need long felt by clinicians. The number of rare diseases concerning which information is made available in this text is astounding. Surgeons, internists and roentgenologists owe a debt of gratitude to the author for this worthwhile accomplishment. It should prove an extremely valuable source book." *Surgery.*

"This is an extremely worthwhile and valuable book which can be recommended without reserve. A book of real value to the gastro-enterologist and radiographer. Indeed the physician in general practice may read it with profit and add it with wisdom to his reference library." *American Journal of Clinical Pathology.*

"It is difficult not to be too laudatory of this book, which is well balanced throughout, well written and splendidly illustrated, and has a comprehensive bibliography. Every roentgenologist should own it. Indeed it would seem to be a necessity for any internist." *New England Journal of Medicine.*

"The book is clear and thorough, it is adequately illustrated, and it will be an invaluable reference work." *Archives of Internal Medicine.*

"An excellent account of the application of roentgenology to the elucidation of diseases of the digestive tract. It covers the whole ground and will be of service to advanced students and practitioners." *British Medical Journal.*

"Not only as a textbook but as a quick, ready and complete reference "Clinical Roentgenology of the Digestive Tract" is an asset to the general practitioner and the radiologist." *Canadian Medical Association Journal.*

The Williams & Wilkins Co.

Publishers of Wm. Wood Books, Baltimore 2, Md.

Please send Feldman: CLINICAL ROENTGENOLOGY OF THE DIGESTIVE TRACT, $7.00.

Signature _____ M.D.

Address _____

SURGERY

Editors: ALTON OCHSNER, M.D., 1430 Tulane Ave., New Orleans, La., and OWEN H. WANGENSTEEN, M.D., University Hospitals, Minneapolis, Minn.

Associate Editor: ALFRED BLALOCK, M.D., Johns Hopkins Hospital, Baltimore, Md.

Published by THE C. V. MOSBY COMPANY, 3207 Washington Blvd., St. Louis 3, U.S.A.

Great Britain Agents: Henry Kimpton, Ltd., 26 Bloomsbury Way, London, W.C.1.
Entered at the Post Office at St. Louis, Mo., as Second-Class Matter.

Published Monthly. Subscriptions may begin at any time.

Editorial Communications

Original Communications.—This Journal invites concise original articles of new matter in the broad field of clinical and experimental surgery. Descriptions of new techniques and methods are welcomed. Articles are accepted for publication with the understanding that they are contributed solely to SURGERY.

Manuscripts submitted for publication may be sent to Dr. Alton Ochsner, 1430 Tulane Avenue, New Orleans, Louisiana, or to Dr. Owen H. Wangensteen, University Hospitals, Minneapolis, Minnesota.

Neither the editors nor the publishers accept responsibility for the views and statements of authors expressed in their communications.

Translations.—Manuscripts written in a foreign language, if found suitable for publication, will be translated without cost to the author.

Manuscripts.—Manuscripts should be typewritten on one side of the paper only, with double spacing and liberal margins. References should be placed at the end of the article and should conform to the style of the Quarterly Cumulative Index Medicus; viz., name of author, title of article, and name of periodical with volume, page, and year. Illustrations accompanying manuscripts should be numbered, provided with suitable legends, and marked on margin or back with the author's name.

Authors should indicate on the manuscript the approximate position of text figures. The original drawings, not photographs of them, should accompany the manuscript.

Illustrations.—A reasonable number of half-tone illustrations will be reproduced free of cost to the author, but special arrangements must be made with the editors for color plates, elaborate tables or extra illustrations. Copy for zinc cuts (such as pen drawings and charts) should be drawn and lettered only in India ink, or black typewriter ribbon (when the typewriter is used), as ordinary blue ink or colors will not reproduce. Only good photographic prints or drawings should be supplied for half-tone work.

Exchanges.—Contributions, letters, exchanges, reprints, and all other communications relating to SURGERY should be sent to one of the editors.

Review of Books.—Books and monographs, native and foreign, will be reviewed according to their merits and as space permits. Books may be sent to Dr. Owen H. Wangensteen, University Hospitals, Minneapolis, Minn.

Reprints.—Reprints of articles published among "Original Communications" must be ordered directly through the publishers, The C. V. Mosby Co., 3207 Washington Blvd., St. Louis 3, U.S.A., who will send their schedule of prices.

Business Communications

Business Communications.—All communications in regard to advertising, subscriptions, change of address, etc., should be addressed to the publishers, The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo.

Subscription Rates.—Single copies, 85 cents. To any place in the United States and its Possessions and the Pan-American Countries, $10.00 per year in advance. To Canada, $11.50 (Canadian Currency), and under foreign postage, $11.00. Includes two volumes a year, January and July.

Remittances.—Remittances for subscriptions should be made by check, draft, post office or express money order, or registered letter, payable to the publishers, The C. V. Mosby Co.

Change of Address.—The publishers should be advised of change of subscriber's address about fifteen days before the date of issue, with both new and old addresses given.

Nonreceipt of Copies.—Complaints for nonreceipt of copies or requests for extra numbers must be received on or before the 10th of the month preceding publication; otherwise the supply is likely to be exhausted.

Advertisements.—Only articles of known scientific value will be given space. Forms close tenth of month preceding date of issue. Advertising rates and page sizes on application.

covering surgical problems which arise in everyday urological practice . . .

AUSTIN I. DODSON'S
UROLOGICAL SURGERY

By **AUSTIN I. DODSON, M.D., F.A.C.S.**

Professor of Urology, Medical College of Virginia; Urologist to the Hospital Division, Medical College of Virginia.

With Contributions by

R. A. BERGER, M.D., DOUGLAS G. CHAPMAN, M.D., EVERETT IDRIS EVANS, Ph.D., M.D., FRED M. HODGES, M.D., MAJOR GUY WINSTON HORSLEY, LINWOOD D. KEYSER, M.D., LAWRENCE O. SNEAD, M.D., F.A.C.R.

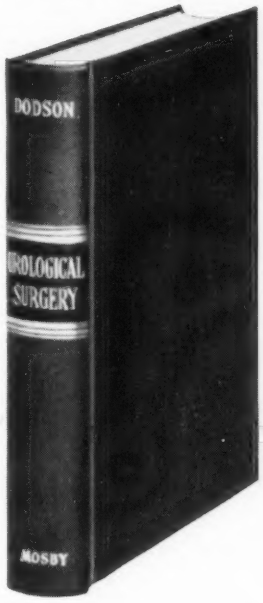
750 pages, 576 illustrations.

RECENTLY PUBLISHED, PRICE, CLOTH, $10.00

Urologist, surgeon and general practitioner will find valuable assistance in this latest contribution of a recognized authority in the field. In UROLOGICAL SURGERY, Dr. Dodson has created a clinical aid as well as a supplement to the ordinary text in urology.

Although primarily concerned with surgery, in order to give the nonspecialist background material, the text includes urological diagnosis and pathology.

Operative procedures are illustrated by Helen Lorraine. Dr. Dodson describes one or more procedures for each surgical problem. They are methods which in his vast experience he has found practical or has determined physiologically sound.



THE C. V. MOSBY COMPANY MJ
3207 Washington Blvd., St. Louis 3, Mo.

Gentlemen: Send me a copy of Dodson's UROLOGICAL SURGERY. The price is $10.00.

☐ Attached is my check. ☐ Charge my account

Dr. _____

Address _____

INDEX TO ADVERTISERS

Please mention "SURGERY" when writing to our advertisers—It identifies you

Abbott Laboratories (Penicillin) ---- 9
American Congress of Obstetrics and Gynecology ---------- 16
Articles to Appear in Early Issues ---------- 3rd Cover

Back Copies Wanted ---------- 20
Burroughs Wellcome & Co. (U.S.A.) Inc. ('Tabloid' 'Ferad' No. 2) ----- 4

Ciba Pharmaceutical Products, Inc. (Nupercainal) ---------- 11

Davis & Geck, Inc. (Sutures) ---------- Insert between pp. 2 and 3

Ethicon Suture Laboratories (Sutures and Needles) ---------- 13

Hoffman-La Roche, Inc. (Prostigmin Methylsulfate) ---------- 4th Cover

Iodine Educational Bureau (Iodine)-- 10

Lilly and Company, Eli (Sulfonamides) ---------- 14
Lippincott Co., J. B. (Surgical Books) 12

Merrell Company, The Wm. S. (Ceepryn) ---------- 15

National Drug Company, The (Allantomide) ---------- 1

Pilling & Son Company, George P. (Instruments) ---------- 5

Scanlan-Morris (Needled Sutures) --- 8
Squibb & Sons, E. R. (Ether) ------ 2
Stearns & Company, Frederick (Biomines Capsules) ---------- 7
Suckert Loose Leaf Cover Company 20

White Laboratories (Vitamin A and D Ointment) ---------- 3
Williams & Wilkins Co., The -------- 17
Wyeth Incorporated (Penicillin Sodium) ---------- 6

All possible care is exercised in the preparation of this index. The publishers are not responsible for any errors or omissions.

A Handsome Permanent Binder for SURGERY

ONLY $1.25

The ONLY binder that opens flat as a bound book! Made of durable imitation leather, it will preserve your journals permanently. Each cover holds 6 issues, one volume (2 volumes published each year). Do your own binding at home in a few minutes. Instructions easy to follow.

Mail coupon for full information and binder on 10-day free trial.

MAIL COUPON TODAY

SUCKERT LOOSE LEAF COVER CO.
234 W. Larned St., Detroit, Michigan

Mail postpaid _____ binders for "SURGERY" for year _____. Will remit in 10 days or return bindings collect.

Name _____

Address _____

Back Issues Wanted

Help other physicians complete their volumes

We will pay 55¢ per copy for the following:

American Journal of Obstetrics & Gynecology
January, February, 1945

Journal of Laboratory & Clinical Medicine
January, February, 1945

The Journal of Pediatrics
January, 1945

American Heart Journal
January, February, March, 1945

Send Journals to Subscription Manager, Dept. A, The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo.

Articles to appear in early issues of

SURGERY

Society of University Surgeons Issue

ELECTIVE OCCLUSION AND EXCISION OF THE PORTAL VEIN.
By Alexander Brunschwig, M.D., Robert Bigelow, M.D., and Sabra Nichols, S.B., Chicago, Ill.

BLAST INJURY OF THE LUNG.
By Leffie M. Carlton, Jr., M.D., Richard A. Rasmussen, M.D., and W. E. Adams, M.D., Chicago, Ill.

LIGATION OF THE INFERIOR VENA CAVA.
By Robert O. Northway, M.D., and Robert W. Buxton, M.D., Ann Arbor, Mich.

METABOLIC ALTERATIONS FOLLOWING THERMAL BURNS. IV. THE EFFECT OF TREATMENT WITH WHOLE BLOOD AND A SALT SOLUTION OR WITH PLASMA FOLLOWING AN EXPERIMENTAL BURN.
By William E. Abbott, M.D., Frieda L. Meyer, John W. Hirshfeld, M.D., and Grace E. Griffin, Detroit, Mich.

THE ROLE OF INFECTION IN SHOCK PRODUCED BY MUSCLE INJURY.
By Earle B. Mahoney, M.D., Joe W. Howland, Ph.D., M.D., and Kathryn Yackel, B.S., Rochester, N. Y.

SUCCINYLSULFATHIAZOLE AND PHTHALYLSULFATHIAZOLE IN SURGERY OF THE COLON.
By Edgar J. Poth, M.D., Ph.D., Galveston, Texas.

HYDRONEPHROSIS. I. THE STRUCTURAL CHANGES.
By Frank Hinman, M.D., San Francisco, Calif.

HYDRONEPHROSIS. II. THE FUNCTIONAL CHANGES.
By Frank Hinman, M.D., San Francisco, Calif.

HYDRONEPHROSIS. III. HYDRONEPHROSIS AND HYPERTENSION.
By Frank Hinman, M.D., San Francisco, Calif.

OSTEOMYELITIS OF THE SKULL—ITS TREATMENT WITH PENICILLIN AND REPAIR OF THE DEFECT WITH TANTALUM.
By Major Max T. Schnitker, Medical Corps, and Captain William D. McCarthy, Dental Corps, Army of the United States.

VIRILISM IN WOMEN.
By Victor Brito, M.D., and A. Rivero, M.D., Caripito, Venezuela.

APPENDICAL PERITONITIS.
By Alton Ochsner, M.D., and J. Harvey Johnston, M.D., New Orleans, La.

CLOSURE OF THE BRONCHIAL STUMP FOLLOWING LOBECTOMY OR PNEUMONECTOMY.
By Richard H. Sweet, M.D., Boston, Mass.

PULSION DIVERTICULUM OF THE HYPOPHARYNX AT THE PHARYNGO-ESOPHAGEAL JUNCTION.
By Stuart W. Harrington, M.D., Rochester, Minn.

THE PRINCIPLE OF EXCISION AND DISSECTION IN CONTINUITY FOR PRIMARY AND METASTATIC MELANOMA OF THE SKIN.
By George T. Pack, M.D., Isabel Scharnagel, M.D., and Mason Morfit, M.D., New York, N. Y.

RADICAL DUODENOPANCREATECTOMY.
By J. E. Strode, M.D., F.A.C.S., Honolulu, Hawaii.

THE TREATMENT OF ADVANCED AND INOPERABLE CANCER.
By William E. Howes, M.D., and Alfred L. Shapiro, M.D., Brooklyn, N. Y.

GANGRENOUS CYSTITIS: ETIOLOGIC CLASSIFICATION AND TREATMENT.
By David S. Cristol, M.D., and Laurence F. Greene, M.D., Rochester, Minn.

"AN AMPUL OF PREVENTION...

— is worth a pound of cure" . . . Postoperative abdominal distention and urinary retention — and the troublesome procedures that follow — are often entirely prevented by the routine use of Prostigmin Methylsulfate 1:4000. Convalescence may be hastened — "gas pains" and the discomforts of catheterization can be eliminated by this simple, effective treatment. Inject 1cc of Prostigmin Methylsulfate 'Roche' 1:4000 at the time of operation and continue with five similar injections at 2-hour intervals after the operation . . . . HOFFMANN-LA ROCHE, INC., ROCHE PARK, NUTLEY 10, NEW JERSEY.

PROSTIGMIN METHYLSULFATE 'ROCHE' 1:4000